

SUBSTITUTED PYRAZOLES

Field of the Invention

5 This invention relates to a series of substituted pyrazoles, pharmaceutical compositions containing these compounds, and intermediates used in their manufacture, and methods of using them.

Background of the Invention

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Cathepsin S (EC 3.4.22.27) is a cysteine protease of the papain family found primarily in lysosomes (Bromme, D.; McGrath, M. E. High Level Expression and Crystallization of Recombinant Human Cathepsin S. *Protein Science* **1996**, 5, 789-791).

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The role of cathepsin S in the immune response is anticipated by its tissue distribution: cathepsin S is found primarily in lymphatic tissues, lymph nodes, the spleen, B lymphocytes, and macrophages (Kirschke, H. Chapter 211. Cathepsin S. In Handbook of Proteolytic Enzymes. Barrett, A. J.; Rawlings, N. D.; Woessner, J. F., Eds. San Diego: Academic Press, 1998. pp. 621-624.). Cathepsin S inhibitors have been shown in animal models to modulate antigen presentation and are effective in an animal model of asthma (Riese, R. J.; Mitchell, R. N.; Villadangos, J. A.; Shi, G.-P.; Palmer, J. T.; Karp, E. R.; De Sanctis, G. T.; Ploegh, H. L.; Chapman, H. A. Cathepsin S Activity
20 Regulates Antigen Presentation and Immunity. *J. Clin. Invest.* **1998**, 101, 2351-2363 and Shi, G.-P.; Villadangos, J. A.; Dranoff, G.; Small, C.; Gu, L.; Haley, K. J.; Riese, R.; Ploegh, H. L.; Chapman, H. A. Cathepsin S Required for Normal MHC Class II Peptide Loading and Germinal Center Development. *Immunity* **1999**, 10, 197-206.).

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Mice in which the gene encoding cathepsin S has been knocked out are less susceptible to collagen-induced arthritis and their immune systems have an impaired ability to respond to antigens (Nakagawa, T. Y.; Brissette, W. H.; Lira, P. D.; Griffiths, R. J.; Petrushova, N.; Stock, J.; McNeish, J. D.; Eastman, S. E.; Howard, E. D.; Clarke, S. R. M.; Rosloniec, E. F.; Elliott, E. A.; Rudensky, A. Y. Impaired Invariant Chain Degradation and Antigen Presentation and Diminished Collagen-Induced Arthritis in Cathepsin S Null Mice. *Immunity* **1999**, *10*, 207-217).

These data demonstrate that compounds that inhibit the proteolytic activity of human cathepsin S should find utility in the treatment of chronic autoimmune diseases including, but not limited to, lupus, rheumatoid arthritis, and asthma; and have potential utility in modulating the immune response to tissue transplantation.

There are a number of cathepsin S inhibitors reported in the literature. The most important patents are listed below.

Certain dipeptidyl nitriles are claimed by Novartis as cathepsin S inhibitors in: Altmann, et. al. WO-99/24460.

Dipeptidyl vinyl sulfones are claimed by Arris (now Axys) as cysteine protease (including cathepsin S) inhibitors in: Palmer, et. al. US-5976858.

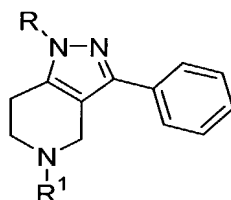
Certain peptidyl sulfonamides are claimed by Arris/Axys as cysteine protease (including cathepsin S) inhibitors in: Palmer, et. al. US-5776718 (assigned to Arris, now Axys) & Klaus, et. al. US-6030946 (assigned to Axys).

Compounds somewhat similar to those of the present invention are described in the following references.

Winters, et. al. (Winters, G.; Sala, A.; Barone, D.; Baldoli, E. *J. Med. Chem.* **1985**, *28*, 934-940; Singh, P.; Sharma, R. C. *Quant. Struct.-Act. Relat.*

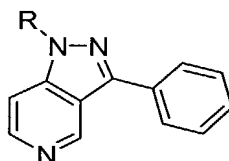
1990, 9, 29-32; Winters, G.; Sala, A.; Barone, D. in US-4500525 (1985)) have described bicyclic pyrazoles of the type shown below. R never contains a heterocyclic ring and no protease inhibitor activity is ascribed to these molecules; they are described as α 1-adrenergic receptor modulators.

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Shutske, et. al. claim the bicyclic pyrazoles below. The pyridine ring is aromatic in their system (Shutske, G. M.; Kapples, K. J.; Tomer, J. D. US-5264576 (1993)). Although reference is made to R being a linker to a heterocycle, the claims specify only R = hydrogen. The compounds are referred to as serotonin reuptake inhibitors.

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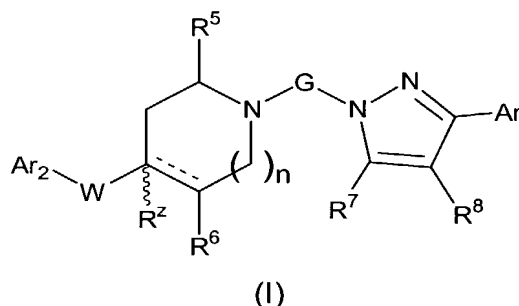
The compound 2-[4-[4-(3-methyl-5-phenyl-1H-pyrazol-1-yl)butyl]-1-piperazinyl]-pyrimidine is known from EP-382637, which describes pyrimidines having anxiolytic properties. This compound and analogs are further described in EP-502786 as cardiovascular and central nervous system agents. Pharmaceutical formulations with such compounds are disclosed in EP-655248 for use in the treatment of gastric secretion and as anti-ulcer agents. WO-9721439 describes medicaments with such compounds for treating obsessive-compulsive disorders, sleep apnea, sexual dysfunctions, emesis and motion sickness.

- The compounds 5-methyl-3-phenyl-1-[4-(4-phenyl-1-piperazinyl)butyl]-1H-indazole and 5-bromo-3-(2-chlorophenyl)-1-[4-(4-phenyl-1-piperazinyl)butyl]-1H-indazole, in particular the hydrochloride salts thereof, are known from WO-9853940 and CA 122:314528, where these and similar
- 5 compounds are described as kinase inhibitors in the former reference and possessing affinity for benzodiazepine receptors in the latter reference.

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Summary of the Invention

The present invention concerns compounds which can be represented
5 by formula (I):



wherein:

Ar₂ is a monocyclic or bicyclic ring system, unsaturated, saturated or
10 aromatic, optionally fused, optionally including between 1 and 5 heteroatom
ring moieties independently selected from O, S, N, SO₂, and C=O; said Ar₂ ring
system being optionally substituted with between 1 and 4 substituents;

R⁵ and R⁶ are independently selected from hydrogen and C₁₋₅ alkyl;
15 R⁷ and R⁸ are independently hydrogen, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₁₋₅ alkoxy, C₁₋₅
alkylthio, halogen, or a 4-7 membered carbocyclyl or heterocyclyl;

alternatively, R⁷ and R⁸ can be taken together to form an optionally substituted
5- to 7- membered carbocyclic or heterocyclic ring, which ring may be
20 unsaturated or aromatic, and may be optionally substituted with between
one and three substituents independently selected from halo, cyano,
amino, hydroxy, nitro, R⁴, R⁴O-, R⁴S-, R⁴O(C₁₋₅ alkylene)-, R⁴O(C=O)-,
R⁴(C=O)-, R⁴(C=S)-, R⁴(C=O)O-, R⁴O(C=O)(C=O)-, R⁴SO₂,
NHR⁴⁴(C=NH)-, NHR⁴⁴SO₂-, and NHR⁴⁴(C=O)-;

R⁴ is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₁₋₅ heterocyclyl, (C₁₋₅ heterocyclyl)C₁₋₆
25 alkylene, phenyl, benzyl, phenethyl, NH₂, mono- or di(C₁₋₆ alkyl)N-, (C₁₋₆
alkoxy)carbonyl- or R⁴²OR⁴³-, wherein R⁴² is H, C₁₋₅ alkyl, C₂₋₅ alkenyl,
phenyl, benzyl, phenethyl, C₁₋₅ heterocyclyl, or (C₁₋₅ heterocyclyl)C₁₋₆

alkylene and R^{43} is C_{1-5} alkylene, phenylene, or divalent C_{1-5} heterocyclyl;

R^{44} can be H in addition to the values for R^4 ;

5 n is 0, 1, or 2;

G is C_{3-6} alkenediyl or C_{3-6} alkanediyl, optionally substituted with hydroxy, halogen, C_{1-5} alkoxy, C_{1-5} alkyl, oxo, hydroximino, CO_2R^k , R^kR^lN , $R^kR^lNCO_2$, (L)- C_{1-4} alkylene-, (L)- C_{1-5} alkoxy, N_3 or [(L)- C_{1-5} alkylene]amino;

10 each of R^k and R^l is independently hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, phenethyl, or C_{1-5} heterocyclyl; alternatively R^k and R^l , can be taken together to form an optionally substituted 4- to 7- membered heterocyclic ring, which ring may be saturated, unsaturated or aromatic;

15 L is amino, mono- or di- C_{1-5} alkylamino, pyrrolidinyl, morpholinyl, piperidinyl, homopiperidinyl, or piperazinyl, wherein available ring nitrogens may be optionally substituted with C_{1-5} alkyl, benzyl, C_{2-5} acyl, C_{1-5} alkylsulfonyl, or C_{1-5} alkoxycarbonyl;

Ar represents a monocyclic or bicyclic aryl or heteroaryl ring, optionally substituted with between 1 and 3 substituents independently selected from
20 halogen, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, cyano, azido, nitro, $R^{22}R^{23}N$, $R^{24}SO_2$, $R^{24}S$, $R^{24}SO$, $R^{24}OC=O$, $R^{22}R^{23}NC=O$, C_{1-5} haloalkyl, C_{1-5} haloalkoxy, C_{1-5} haloalkylthio, and C_{1-5} alkylthio;

25 R^{22} is hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, phenethyl, benzyl, or C_{1-5} heterocyclyl, C_{2-8} acyl, aroyl, $R^{38}OC=O$, $R^{25}R^{26}NC=O$, $R^{38}SO$, $R^{38}SO_2$, $R^{38}S$, or $R^{25}R^{26}NSO_2$;

R^{23} is hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl or C_{1-5} heterocyclyl; alternatively, R^{22} and R^{23} can be taken together to form an optionally substituted 4- to 7- membered heterocyclic ring, which ring may be
30 saturated, unsaturated or aromatic;

each of R^{24} and R^{24} is C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, or C_{1-5} heterocyclyl;

R^{25} and R^{26} independently are hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, or C_{1-5} heterocyclyl;

or, alternatively, R^{25} and R^{26} can be taken together to form an optionally substituted 4- to 7-membered heterocyclic ring, which ring may be saturated, unsaturated or aromatic;

W represents O, S, NR^{27} , C=O, (C=O)NH, NH(C=O), CHR^{28} , or a covalent bond;

R^z is H or OH and the dashed line is absent; or R^z is absent where the dashed line is an sp^2 bond;

R^{27} is hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, naphthyl, benzyl, phenethyl, C_{1-5} heterocyclyl, C_{2-8} acyl, aroyl, $R^{29}OC=O$, $R^{30}R^{31}NC=O$, $R^{29}SO$, $R^{29}S$, $R^{29}SO_2$, or $R^{30}R^{31}NSO_2$;
or, alternatively, R^{27} and part of Ar_2 can be taken together to form an optionally substituted 5- or 6-membered heterocyclic ring with optionally 1 to 3 additional heteroatom moieties in the ring selected from O, NR^9 , NR^{10} , N, SO_2 , C=O, and S; which ring may be saturated, unsaturated or aromatic; R^9 and R^{10} are independently selected from H, C_{1-3} alkyl, and $-CH_2CO_2(C_{1-4}$ alkyl);

R^{28} is hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, hydroxy, phenyl, benzyl, C_{1-5} heterocyclyl, $R^{29}O$, $R^{30}R^{31}NC=O$, $R^{29}S$, $R^{29}SO$, $R^{29}SO_2$, or $R^{30}R^{31}NSO_2$;

R^{29} is C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, or C_{1-5} heterocyclyl;
 R^{30} and R^{31} are independently selected from hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, phenethyl, naphthyl, and C_{1-5} heteroaryl; alternatively, R^{30} and R^{31} can be taken together to form an optionally substituted 4- to 7-membered ring carbocyclic or heterocyclic ring, which ring may be saturated, unsaturated or aromatic;

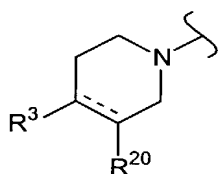
wherein each of the above hydrocarbyl or heterocarbyl groups, unless otherwise indicated, and in addition to any specified substituents, is optionally and independently substituted with between 1 and 3 substituents selected from methyl, halomethyl, hydroxymethyl, halo, hydroxy, amino, nitro, cyano, C_{1-5} alkyl, C_{1-5} alkoxy, $-COOH$, C_{2-6} acyl,

[di(C₁₋₄ alkyl)amino]C₂₋₅ alkylene, [di(C₁₋₄ alkyl)amino] C₂₋₅ alkyl-NH-CO-, and C₁₋₅ haloalkoxy;

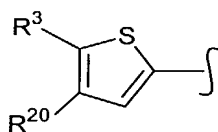
or a pharmaceutically acceptable salt, amide, or ester thereof; or a stereoisomeric form thereof.

- 5 One embodiment of the invention is a compound of formula(I), wherein Ar₂ is selected from 5-7 membered monocyclic rings, and [5,6], [6,6], [6,5], and [5,5] fused bicyclic ring systems, said ring or ring system being carbocyclic or heterocyclic, saturated, unsaturated, or aromatic, optionally substituted with halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, nitro, hydroxy, amino, mono-
 10 or di-(C₁₋₆ alkyl)amino, C₁₋₄ alkoxy, C₂₋₄ alkoxycarbonyl, C₂₋₆ acyl, C₂₋₆ acyloxy, C₁₋₅ alkylsulfonyl, C₁₋₅ alkoxycarbonylC₁₋₄ alkoxy, cyano, and mono- or di-(C₁₋₆ alkyl)carbamoyl.

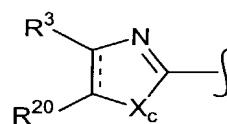
- Another embodiment of the invention is a compound of formula (I), wherein Ar₂ is selected from 2,5-di(C₁₋₆ alkyl)aminopyrrolyl and the following 6
 15 formulae:



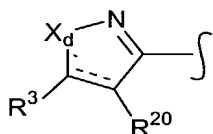
(a)



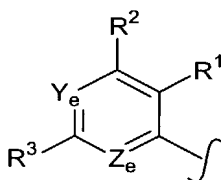
(b)



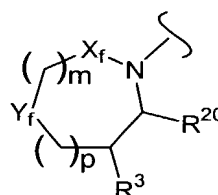
(c)



(d)



(e)



(f)

wherein

each dashed line may be an sp² bond or absent;

X_c is O, S, or N; and X_d is O or S;

- R^1 is hydrogen, halogen, C_{1-5} alkoxy, hydroxy, C_{1-5} alkyl, C_{2-5} alkenyl, cyano, nitro, $R^a R^b N$, C_{2-8} acyl, C_{1-5} heterocyclyl, (C_{1-5} heterocyclyl) C_{1-5} alkylene, $R^{11}S$, $R^{11}SO$, $R^{11}SO_2$, $R^c OC=O$, $R^c R^d NC=O$, or $R^c R^d NSO_2$; or R^1 can be taken together with R^{27} as provided below;
- R^2 is hydrogen, halogen, C_{1-5} alkoxy, hydroxy, C_{1-5} alkyl, C_{2-5} alkenyl, cyano, nitro, $R^e R^f N$, C_{1-5} heterocyclyl, or C_{2-8} acyl;
- R^3 is hydrogen, halogen, C_{1-5} alkoxy, hydroxy, C_{1-5} alkyl, C_{2-5} alkenyl, cyano, nitro, $R^g R^h N$, C_{2-8} acyl, C_{1-5} heterocyclyl, $R^i OC=O$, $R^g R^h NC=O$, or $R^g R^h NSO_2$;
- R^a is selected from hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, phenethyl, C_{1-5} heterocyclyl, C_{2-8} acyl, aroyl, $R^j OC=O$, $R^i R^j NC=O$, $R^{12}SO$, $R^{12}SO_2$, $R^{12}S$, and $R^i R^j NSO_2$;
- R^e is selected from hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, phenethyl, C_{1-5} heterocyclyl, C_{2-8} acyl, aroyl, $R^{32} OC=O$, $R^{32} R^{33} NC=O$, $R^{13}SO$, $R^{13}SO_2$, $R^{13}S$, and $R^{32} R^{33} NSO_2$;
- R^m is selected from hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, phenethyl, C_{1-5} heterocyclyl, C_{2-8} acyl, aroyl, $R^{34} OC=O$, $R^{34} R^{35} NC=O$, $R^{15}SO$, $R^{15}SO_2$, $R^{15}S$, and $R^{34} R^{35} NSO_2$;
- R^o is selected from hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, phenethyl, C_{1-5} heterocyclyl, C_{2-8} acyl, aroyl, $R^{36} OC=O$, $R^{36} R^{37} NC=O$, $R^{19}SO$, $R^{19}SO_2$, $R^{19}S$, and $R^{36} R^{37} NSO_2$;
- each of R^b , R^f , R^n , R^p , R^{32} , R^{33} , R^{34} , R^{35} , R^{36} , R^{37} , R^{39} , and R^{40} is independently selected from hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, phenethyl, and C_{1-5} heteroaryl;
- alternatively, R^a and R^b , R^e and R^f , R^m and R^n , and R^o and R^p , independently, can be taken together to form an optionally substituted 4- to 7- membered heterocyclic ring, which ring may be saturated, unsaturated or aromatic;
- each of R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{19} , R^{38} , and R^{41} is independently C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, phenethyl, or C_{1-5} heterocyclyl;
- each of R^c and R^d , and R^i and R^j are independently are hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, phenethyl, or C_{1-5} heteroaryl; alternatively, R^c and R^d , and R^i and R^j , independently, can be taken together to form

- an optionally substituted 4- to 7- membered heterocyclic ring, which ring may be saturated, unsaturated or aromatic;
- R^g is hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, phenethyl, C_{1-5} heterocyclyl, C_{2-8} acyl, aroyl, $R^{17}OC=O$, $R^{17}R^{18}NC=O$, $R^{16}S$, $R^{16}SO$, $R^{16}SO_2$, or $R^{17}R^{18}NSO_2$;
- R^h is hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, phenethyl or C_{1-5} heterocyclyl; alternatively, R^g and R^h can be taken together to form an optionally substituted 4- to 7- membered heterocyclic ring, which ring may be saturated, unsaturated or aromatic;
- R^{17} and R^{18} independently are hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, benzyl, or C_{1-5} heterocyclyl; alternatively, R^{17} and R^{18} can be taken together to form an optionally substituted 4- to 7- membered heterocyclic ring, which ring may be saturated, unsaturated or aromatic;
- Y_e is nitrogen or $R^{20}C$;
- Z_e is nitrogen or $R^{21}C$;
- R^{20} is hydrogen, halogen, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, cyano, nitro, R^mR^nN , C_{2-8} acyl, $R^mOC=O$, $R^{14}S$, $R^{14}SO$, or $R^{14}SO_2$;
- R^{21} is hydrogen, halogen, C_{1-5} alkoxy, C_{1-5} alkyl, C_{2-5} alkenyl, cyano, nitro, R^oR^pN , C_{2-8} acyl, $R^{16}OC=O$, $R^{11}S$, $R^{11}SO$, or $R^{11}SO_2$;
- alternatively, R^3 and R^{20} or R^3 and R^{21} can be taken together to form an optionally substituted 5- or 6-membered carbocyclic or heterocyclic ring, which ring may be saturated, unsaturated or aromatic; wherein said ring may be optionally substituted with halo, di(C_{1-5} alkyl)amino, C_{2-5} acyl, and C_{1-5} alkoxy;
- R^{27} is hydrogen, C_{1-5} alkyl, C_{3-5} alkenyl, phenyl, naphthyl, benzyl, phenethyl, C_{1-5} heterocyclyl, C_{2-8} acyl, aroyl, $R^{29}OC=O$, $R^{30}R^{31}NC=O$, $R^{29}SO$, $R^{29}S$, $R^{29}SO_2$, or $R^{30}R^{31}NSO_2$;

or, alternatively, R^{27} and R^1 can be taken together to form an optionally substituted 5- or 6-membered heterocyclic ring with optionally 1 to 3 additional heteroatom moieties in the ring selected from O, NR^9 , NR^{10} , N, SO_2 , $C=O$, and S; which ring may be saturated, unsaturated or aromatic; R^9 and R^{10} are independently selected from H, C_{1-3} alkyl, and $-CH_2CO_2(C_{1-4}$ alkyl);

X_f is CHR^{1f} , $=N-$, NH , $C=O$, SO_2 , $CHSR^{1f}$ wherein, in formula (f), R^{1f} is hydrogen, halogen, C_{1-5} alkoxy, hydroxy, C_{1-5} alkyl, C_{3-5} alkenyl, cyano, nitro, $R^{39}R^{40}N$, C_{2-8} acyl, C_{1-5} heterocyclyl, $(C_{1-5}$ heterocyclyl) C_{1-5} alkylene, $R^{41}S$, $R^{41}SO$, $R^{41}SO_2$, $R^{39}OC=O$, $R^{39}R^{40}NC=O$, $R^{39}R^{40}NSO_2$, $R^{41}SO_3^-$ or $R^{39}(C=O)O^-$;

Y_f is CH_2 , CHR^{2f} , $=CR^{2f}$, O, or NR^{2f} , wherein R^{2f} is H, C_{1-7} alkyl, C_{3-5} alkenyl, C_{2-8} acyl, C_{1-5} heterocyclyl, $(C_{1-5}$ heterocyclyl)- C_{1-5} alkylene, phenyl, (phenyl)- C_{1-5} alkylene, $(C_{3-7}$ cycloalkyl)- C_{1-5} alkylene, $(H_2NCO)-C_{1-5}$ alkylene, C_{1-5} haloalkyl, C_{1-5} cyanoalkyl, $(C_{1-5}$ alkoxy carbonyl) C_{1-5} alkylene, and (phenylcarbonyl)NH-;

m is 0 or 1;

p is 0 or 1;

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wherein each of the above hydrocarbonyl or heterocarbonyl groups, unless otherwise indicated, and in addition to any specified substituents, is optionally and independently substituted with between 1 and 3 substituents selected from methyl, halomethyl, hydroxymethyl, halo, hydroxy, amino, nitro, cyano, C_{1-5} alkyl, C_{1-5} alkoxy, $-COOH$, C_{2-6} acyl, $[di(C_{1-4}$ alkyl)amino] C_{2-5} alkylene, $[di(C_{1-4}$ alkyl)amino] C_{2-5} alkyl-NH-CO-, and C_{1-5} haloalkoxy.

The disclosed compounds are high-affinity inhibitors of the proteolytic activity of human cathepsin S. For use in medicine, the preparation of pharmaceutically acceptable salts of compounds of formula (I) may be desirable.

Certain compounds of the present invention may have one stereogenic atom and may exist as two enantiomers. Certain compounds of the present invention may have two or more stereogenic atoms and may further exist as diastereomers. It is to be understood by those skilled in the art that all such stereoisomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Another aspect of the invention provides pharmaceutical compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier. A further embodiment of the invention is a process for making a pharmaceutical composition comprising mixing a disclosed compound as described above, with a suitable pharmaceutically acceptable carrier.

The invention also contemplates pharmaceutical compositions comprising more than one compound of formula (I) and compositions comprising a compound of formula (I) and another pharmaceutically active agent.

The invention features a method of treating disorders or conditions mediated by the cathepsin S enzyme, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above. If more than one active agent is administered, the therapeutically effective amount may be a jointly effective amount. The compounds described herein inhibit the protease activity of human cathepsin S, an enzyme involved in the immune response. In preferred embodiments, cathepsin S inhibition is selective. As such, the disclosed compounds and compositions are useful in the prevention, inhibition, or treatment of autoimmune diseases such as lupus, rheumatoid arthritis, and asthma, and for the prevention, inhibition, or treatment of tissue transplant rejection.

[illegible]

Detailed Description of the Invention

The invention features pyrazole compounds of formula (I), methods of making them, compositions containing them, and methods of using them to treat diseases and conditions, including those mediated by Cathepsin S.

A. Terms

The following terms are defined below and by their usage throughout this disclosure.

“Alkyl” includes optionally substituted straight chain and branched hydrocarbons with at least one hydrogen removed to form a radical group. Alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, 1-methylpropyl, pentyl, isopentyl, sec-pentyl, hexyl, heptyl, octyl, and so on. Alkyl includes cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

“Alkenyl” includes optionally substituted straight chain and branched hydrocarbon radicals as above with at least one carbon-carbon double bond (sp^2). Alkenyls include ethenyl (or vinyl), prop-1-enyl, prop-2-enyl (or allyl), isopropenyl (or 1-methylvinyl), but-1-enyl, but-2-enyl, butadienyls, pentenyls, hexa-2,4-dienyl, and so on. Hydrocarbon radicals having a mixture of double bonds and triple bonds, such as 2-penten-4-ynyl, are grouped as alkynyls herein. Alkenyl includes cycloalkenyl. *Cis* and *trans* or (E) and (Z) forms are included within the invention.

“Alkynyl” includes optionally substituted straight chain and branched hydrocarbon radicals as above with at least one carbon-carbon triple bond (sp). Alkynyls include ethynyl, propynyls, butynyls, and pentynyls. Hydrocarbon radicals having a mixture of double bonds and triple bonds, such as 2-penten-4-ynyl, are grouped as alkynyls herein. Alkynyl does not include cycloalkynyl.

“Alkoxy” includes an optionally substituted straight chain or branched alkyl group with a terminal oxygen linking the alkyl group to the rest of the molecule. Alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy and so on. “Aminoalkyl”, “thioalkyl”, and “sulfonylalkyl” are analogous to alkoxy, replacing the terminal oxygen atom of alkoxy with, respectively, NH (or NR), S, and SO₂. Heteroalkyl includes alkoxy, aminoalkyl, thioalkyl, and so on.

“Aryl” includes phenyl, naphthyl, biphenyl, tetrahydronaphthyl, and so on, any of which may be optionally substituted. Aryl also includes arylalkyl groups such as benzyl, phenethyl, and phenylpropyl. Aryl includes a ring system containing an optionally substituted 6-membered carbocyclic aromatic ring, said system may be bicyclic, bridge, and/or fused. The system may include rings that are aromatic, or partially or completely saturated. Examples of ring systems include indenyl, pentalenyl, 1-4-dihydronaphthyl, indanyl, benzimidazolyl, benzothiophenyl, indolyl, benzofuranyl, isoquinolinyl, and so on.

“Heterocyclyl” includes optionally substituted aromatic and nonaromatic rings having carbon atoms and at least one heteroatom (O, S, N) or heteroatom moiety (SO₂, CO, CONH, COO) in the ring. Unless otherwise indicated, a heterocyclic radical may have a valence connecting it to the rest of the molecule through a carbon atom, such as 3-furyl or 2-imidazolyl, or through a heteroatom, such as N-piperidyl or 1-pyrazolyl. Preferably a monocyclic heterocyclyl has between 4 and 7 ring atoms, or between 5 and 6 ring atoms; there may be between 1 and 5 heteroatoms or heteroatom moieties in the ring, and preferably between 1 and 3. A heterocyclyl may be saturated, unsaturated, aromatic (e.g., heteroaryl), nonaromatic, or fused.

30

Heterocyclyl also includes fused, e.g., bicyclic, rings, such as those optionally condensed with an optionally substituted carbocyclic or heterocyclic five- or six-membered aromatic ring. For example, “heteroaryl” includes an

optionally substituted six-membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms condensed with an optionally substituted five- or six-membered carbocyclic or heterocyclic aromatic ring. Said heterocyclic five- or six-membered aromatic ring condensed with the said five- or six-membered aromatic ring may contain 1, 2 or 3 nitrogen atoms where it is a six-membered ring, or 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulfur where it is a five-membered ring.

Examples of heterocyclyls include thiazoylyl, furyl, pyranlyl, isobenzofuranyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indoliziny, isoindolyl, indolyl, indazolyl, purinyl, quinolyl, furazanyl, pyrrolidinyl, pyrrolinyl, imdazolidinyl, imidazoliny, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, and morpholinyl. For example, preferred heterocyclyls or heterocyclic radicals include morpholinyl, piperazinyl, pyrrolidinyl, pyridyl, cyclohexylimino, cycloheptylimino, and more preferably, piperidyl.

Examples illustrating heteroaryl are thienyl, furanyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, benzothienyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl.

"Acyl" refers to a carbonyl moiety attached to either a hydrogen atom (i.e., a formyl group) or to an optionally substituted alkyl or alkenyl chain, or heterocyclyl.

"Halo" or "halogen" includes fluoro, chloro, bromo, and iodo, and preferably chloro or bromo as a substituent.

"Alkanediyl" or "alkylene" represents straight or branched chain optionally substituted bivalent alkane radicals such as, for example, methylene, ethylene, propylene, butylene, pentylene or hexylene.

"Alkenediyl" represents, analogous to the above, straight or branched chain optionally substituted bivalent alkene radicals such as, for example, propenylene, butenylene, pentenylene or hexenylene. In such radicals, the carbon atom linking a nitrogen preferably should not be unsaturated.

5

"Aroyl" refers to a carbonyl moiety attached to an optionally substituted aryl or heteroaryl group, wherein aryl and heteroaryl have the definitions provided above. In particular, benzoyl is phenylcarbonyl.

10 As defined herein, two radicals, together with the atom(s) to which they are attached may form an optionally substituted 4- to 7-, 5 - to 7-, or a 5- to 6-membered ring carbocyclic or heterocyclic ring, which ring may be saturated, unsaturated or aromatic. Said rings may be as defined above in the Summary of the Invention section. Particular examples of such rings are as follows in the
15 next section.

"Pharmaceutically acceptable salts, esters, and amides" include carboxylate salts (e.g., C₁₋₈ alkyl, cycloalkyl, aryl, heteroaryl, or non-aromatic heterocyclic) amino acid addition salts, esters, and amides which are within a
20 reasonable benefit/risk ratio, pharmacologically effective and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. Representative salts include hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate,
25 succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulfonate. These may include alkali metal and alkali earth cations such as sodium, potassium, calcium, and magnesium, as well as non-toxic ammonium, quaternary ammonium, and amine cations such as tetramethyl ammonium, methylamine, trimethylamine, and ethylamine. See example, S.M.
30 Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977, 66:1-19 which is incorporated herein by reference. Representative pharmaceutically acceptable amides of the invention include those derived from ammonia, primary C₁₋₆ alkyl amines and secondary di (C₁₋₆ alkyl) amines. Secondary amines include 5- or

6-membered heterocyclic or heteroaromatic ring moieties containing at least one nitrogen atom and optionally between 1 and 2 additional heteroatoms. Preferred amides are derived from ammonia, C₁₋₃ alkyl primary amines, and di (C₁₋₂ alkyl)amines. Representative pharmaceutically acceptable esters of the
5 invention include C₁₋₇ alkyl, C₅₋₇ cycloalkyl, phenyl, and phenyl(C₁₋₆)alkyl esters. Preferred esters include methyl esters.

“Patient” or “subject” includes mammals such as humans and animals (dogs, cats, horses, rats, rabbits, mice, non-human primates) in need of
10 observation, experiment, treatment or prevention in connection with the relevant disease or condition. Preferably, the patient or subject is a human.

“Composition” includes a product comprising the specified ingredients in the specified amounts as well as any product which results directly or
15 indirectly from combinations of the specified ingredients in the specified amounts.

“Therapeutically effective amount” or “effective amount” means that amount of active compound or pharmaceutical agent that elicits the biological or
20 medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

Concerning the various radicals in this disclosure and in the claims,
25 three general remarks are made. The first remark concerns valency. As with all hydrocarbon radicals, whether saturated, unsaturated or aromatic, and whether or not cyclic, straight chain, or branched, and also similarly with all heterocyclic radicals, each radical includes substituted radicals of that type and monovalent, bivalent, and multivalent radicals as indicated by the context of
30 the claims. The context will indicate that the substituent is an alkylene or hydrocarbon radical with at least two hydrogen atoms removed (bivalent) or more hydrogen atoms removed (multivalent). An example of a bivalent radical linking two parts of the molecule is G in formula (I) which links two rings.

Second, radicals or structure fragments as defined herein are understood to include substituted radicals or structure fragments. Hydrocarbyls include monovalent radicals containing carbon and hydrogen such as alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl (whether aromatic or unsaturated), as well as corresponding divalent radicals such as alkylene, alkenylene, phenylene, and so on. Heterocarbyls include monovalent and divalent radicals containing carbon, hydrogen, and at least one heteroatom. Examples of monovalent heterocarbyls include acyl, acyloxy, alkoxyacyl, heterocyclyl, heteroaryl, aroyl, benzoyl, dialkylamino, hydroxyalkyl, and so on.

Using "alkyl" as an example, "alkyl" should be understood to include substituted alkyl having one or more substitutions, such as between 1 and 5, 1 and 3, or 2 and 4 substituents. The substituents may be the same (dihydroxy, dimethyl), similar (chlorofluoro), or different (chlorobenzyl- or aminomethyl-substituted). Examples of substituted alkyl include haloalkyl (such as fluoromethyl, chloromethyl, difluoromethyl, perchloromethyl, 2-bromoethyl, perfluoromethyl, and 3-iodocyclopentyl), hydroxyalkyl (such as hydroxymethyl, hydroxyethyl, 2-hydroxypropyl, aminoalkyl (such as aminomethyl, 2-aminoethyl, 3-aminopropyl, and 2-aminopropyl), nitroalkyl, alkylalkyl, and so on. A di(C₁₋₆ alkyl)amino group includes independently selected alkyl groups, to form, for example, methylpropylamino and isopropylmethylamino, in addition dialkylamino groups having two of the same alkyl group such as dimethyl amino or diethylamino.

Third, only stable compounds are intended. For example, where there is an NR'R" group, and R can be an alkenyl group, the double bond is at least one carbon removed from the nitrogen to avoid enamine formation. Similarly, where a dashed line is an optional sp² bond, if it is absent, the appropriate hydrogen atom(s) is(are) included.

Preferred substitutions for Ar or Ar_i include methyl, methoxy, fluoromethyl, difluoromethyl, perfluoromethyl (trifluoromethyl), 1-fluoroethyl, 2-fluoroethyl, ethoxy, fluoro, chloro, and bromo, and particularly methyl, bromo,

chloro, perfluoromethyl, perfluoromethoxy, methoxy, and fluoro. Preferred substitution patterns for Ar or Ar₁ are 4-substituted or 3,4-disubstituted phenyl.

Compounds of the invention are further described in the next section.

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B. Compounds

The invention features compounds of formula (I) as described in the Summary section.

5

Preferred compounds include those wherein:

- (a) Ar_2 is selected from formulae (e);
- (b) Ar_2 is selected from formulae (f);
- 10 (c) Ar_2 is selected from formula (a)-(d);
- (d) R^1 is halogen, C_{1-5} alkoxy, hydroxy, C_{1-5} alkyl, cyano, nitro, $\text{R}^a\text{R}^b\text{N}$ or is taken together with R^{27} ;
- (e) R^1 is taken together with R^{27} ;
- (f) R^1 and R^{27} taken together are selected from:
- 15 (1) $-\text{CH}_2\text{NR}^9-(\text{C}=\text{O})-$
- (2) $\text{OCH}_2(\text{C}=\text{O})-$
- (3) $-\text{CH}_2\text{CH}_2(\text{C}=\text{O})-$
- (4) $-\text{CH}_2-\text{O}(\text{C}=\text{O})-$
- (5) $-\text{CH}_2\text{S}(\text{C}=\text{O})-$
- 20 (6) $-\text{O}(\text{C}=\text{O})-$
- (7) $-\text{CH}_2(\text{C}=\text{O})-$
- (8) $-\text{NR}^9(\text{C}=\text{O})-$
- (9) $-\text{NR}^9(\text{SO}_2)-$
- (10) $-\text{CH}_2\text{NR}^9\text{SO}_2-$
- 25 (11) $-\text{NR}^9\text{CH}_2(\text{C}=\text{O})-$ and $-\text{SCH}_2(\text{C}=\text{O})-$
- (g) R^1 and R^{27} taken together are selected from:
- a) $-\text{CH}_2-(\text{C}=\text{O})-$
- b) $-\text{O}(\text{C}=\text{O})-$
- c) $-\text{CH}_2\text{CH}_2-$
- 30 d) $-\text{S}(\text{C}=\text{O})-$
- e) $-\text{N}=\text{N}-$
- f) $-\text{NR}^9\text{SO}_2-$
- g) $-\text{N}=\text{CR}^9-$

h) $\text{--NR}^g(\text{C=O})\text{--}$ and

i) --CH=CH-- ;

(h) R^2 is hydrogen, halogen, C_{1-5} alkoxy, C_{1-5} alkyl, cyano, or $\text{R}^e\text{R}^f\text{N}$, where R^e and R^f are H or C_{1-5} alkyl, or are taken together to form a 5-7 membered heterocyclic ring;

(i) R^3 is hydrogen, halogen, C_{1-5} alkoxy, C_{1-5} alkyl, cyano, nitro, or $\text{R}^g\text{R}^h\text{N}$, where R^e and R^f are H or C_{1-5} alkyl, or are taken together to form a 5-7 membered heterocyclic ring;

(j) R^5 and R^6 are independently selected from hydrogen and C_{1-3} alkyl;

(k) one of R^5 and R^6 is H;

(l) R^5 and R^6 are each H;

(m) one of R^7 and R^8 is H and the other is 5-7 membered carbocyclyl or heterocyclyl;

(n) R^7 and R^8 are taken together to form an optionally substituted 5- to 7-membered carbocyclic or heterocyclic ring;

(o) R^7 and R^8 taken together form a six-membered heterocyclyl;

(p) R^7 and R^8 taken together form pyridinyl, pyrimidinyl, or piperazinyl, optionally N-substituted with --(C=O)R^4 , $\text{--SO}_2\text{R}^4$, or --(C=O)NHR^{44} ;

(q) each of R^a , R^e , R^m , and R^o is independently selected from hydrogen, C_{1-5} alkyl, C_{2-8} acyl, and the respective ROC=O , RRNC=O , RSO , RSO_2 , and RRNSO_2 groups;

(r) each of R^a , R^e , R^m , R^o , R^b , R^f , R^n , and R^p is independently selected from hydrogen and C_{1-5} alkyl; or, independently, R^a and R^b , R^e and R^f , R^m and R^n , and R^o and R^p , taken together, form an optionally substituted 4- to 7-membered carbocyclic or heterocyclic ring;

(s) (1) R^a and R^b taken together are independently morpholinyl, piperidinyl, or pyrrolidinyl; (2) R^e and R^f taken together are morpholinyl, piperidinyl, or pyrrolidinyl; or (3) both (1) and (2) apply;

(t) each of R^c and R^d , R^i and R^j , R^k and R^l is independently hydrogen or C_{1-5} alkyl, alternatively, R^c and R^d , R^i and R^j , and R^k and R^l , independently, can be taken together to form an optionally substituted 4- to 7-membered heterocyclic ring, which ring may be saturated, unsaturated or aromatic;

- (u) R^c and R^d , R^i and R^j , and R^k and R^l , independently, are taken together to form an optionally substituted 4- to 7- membered heterocyclic ring, which ring may be saturated, unsaturated or aromatic;
- (v) each of R^b , R^f , R^n , R^p , R^{32} , R^{33} , R^{34} , R^{35} , R^{36} , R^{37} , R^{39} , and R^{40} is independently H or C_{1-5} alkyl;
- (w) each of R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{19} , R^{38} , and R^{41} is independently H or C_{1-5} alkyl;
- (x) R^g is C_{1-5} alkyl, C_{2-8} acyl, $R^{17}OC=O$, $R^{17}R^{18}NC=O$, $R^{16}S$, $R^{16}SO$, $R^{16}SO_2$, or $R^{17}R^{18}NSO_2$; and R^h hydrogen or C_{1-5} alkyl; alternatively, R^g and R^h can be taken together to form an optionally substituted 4- to 7- membered heterocyclic ring;
- (y) R^{17} and R^{18} independently are hydrogen or C_{1-5} alkyl;
- (z) n is 1;
- (aa) n is 0;
- (bb) G is C_{3-4} alkanediyl, optionally substituted with hydroxy, halogen, (L)- C_{1-5} alkyloxy, or [(L)- C_{1-5} alkylene]amino;
- (cc) G is C_3 alkanediyl, optionally substituted with hydroxy, (L)- C_{1-5} alkyloxy, or [(L)- C_{1-5} alkylene]amino;
- (dd) each of R^{20} and R^{21} is independently selected from hydrogen, halogen, C_{1-5} alkoxy, C_{1-5} alkyl, cyano, nitro, and R^mR^nN or R^oR^pN , respectively;
- (ee) each of R^{20} and R^{21} is independently selected from hydrogen, halogen, C_{1-3} alkyl, and R^mR^nN or R^oR^pN , respectively;
- (ff) Ar represents a monocyclic ring, optionally substituted with 1 to 2 substituents selected from halogen, C_{1-5} alkyl, cyano, azido, nitro, $R^{22}R^{23}N$, halomethyl, and halomethoxy;
- (gg) Ar is a six membered ring substituted with between 1 and 2 substituents independently selected from methyl, halogen, CF_3 , and OCF_3 , said substituent or substituents being at the 4- position, or at the 3- and 4- positions, respectively;
- (hh) each of R^{22} , R^{23} , and R^{24} is hydrogen or C_{1-5} alkyl;
- (ii) R^{25} and R^{26} independently are hydrogen or C_{1-5} alkyl; or, alternatively, R^{25} and R^{26} can be taken together to form an optionally substituted 4- to 7- membered heterocyclic ring;

- (jj) each of R^{25} and R^{26} is independently hydrogen or C_{1-5} alkyl;
- (kk) W is NR^{27} ;
- (ll) W is CHR^{28} , and R^{28} is hydrogen or C_{1-5} alkyl;
- (mm) R^{29} is C_{1-5} alkyl; or R^{30} and R^{31} are independently selected from hydrogen
 5 and C_{1-5} alkyl, or R^{30} and R^{31} are taken together to form a 5-6 membered heterocyclcyl;
- (nn) Ar_2 is formula (e) and R^1 is halogen, C_{1-5} alkoxy, hydroxy, C_{1-5} alkyl, cyano, nitro, and R^aR^bN , or R^1 can be taken together with R^{27} as provided below; R^2 is hydrogen, halogen, C_{1-5} alkoxy, C_{1-5} alkyl, or R^eR^fN ; R^3 is
 10 hydrogen, halogen, C_{1-5} alkoxy, hydroxy, C_{1-5} alkyl, cyano, R^gR^hN ; R^5 and R^6 are independently selected from hydrogen and C_{1-3} alkyl;
- (oo) R^7 and R^8 independently are taken together to form an optionally substituted 5- to 7- membered carbocyclic or heterocyclic ring, which ring may be saturated, unsaturated or aromatic;
- (pp) each of R^a , R^e , R^m , and R^o is independently selected from hydrogen, C_{1-5} alkyl, C_{2-8} acyl, and the respective $ROC=O$, $RRNC=O$, RS , RSO , RSO_2 , and $RRNSO_2$ groups;
- (qq) each of R^b , R^f , R^n , and R^p , is independently selected from hydrogen and C_{1-5} alkyl; each of R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{19} , and R^{38} is independently
 20 C_{1-5} alkyl; each of R^c and R^d , R^i and R^j , R^k and R^l , R^{32} and R^{33} , R^{34} and R^{35} , R^{36} and R^{37} are independently are hydrogen or C_{1-5} alkyl, or are taken together to form an optionally substituted 4- to 7- membered heterocyclic ring;
- (rr) R^9 is hydrogen, C_{1-5} alkyl, C_{2-8} acyl, $R^{17}OC=O$, $R^{17}R^{18}NC=O$, $R^{16}S$, $R^{16}SO$,
 25 $R^{16}SO_2$, or $R^{17}R^{18}NSO_2$; R^h is hydrogen or C_{1-5} alkyl; alternatively, R^9 and R^h can be taken together to form an optionally substituted 4- to 7- membered heterocyclic ring; R^{17} and R^{18} independently are hydrogen or C_{1-5} alkyl; n is 0 or 1;
- (ss) G is C_{3-4} alkenediyl or C_{3-4} alkanediyl, optionally substituted with hydroxy,
 30 halogen, C_{1-5} alkyloxy, (L)- C_{1-5} alkoxy, or [(L)- C_{1-5} alkylene]amino; L is amino, mono- or di- C_{1-5} alkylamino, pyrrolidinyl, morpholinyl, piperidinyl homopiperidinyl, or piperazinyl, wherein available ring nitrogens may be

optionally substituted with C_{1-5} alkyl, benzyl, C_{1-5} alkylcarbonyl, or C_{1-5} alkyloxycarbonyl;

(tt) Y_e is nitrogen or $R^{20}C$; Z_e is nitrogen or $R^{21}C$;

(uu) R^{20} and R^{21} are independently selected from hydrogen, halogen, C_{1-5} alkoxy, C_{1-5} alkyl, cyano, nitro, and R^mR^nN or R^oR^pN , respectively; alternatively, R^3 and R^{20} or R^3 and R^{21} can be taken together to form an optionally substituted 5- or 6-membered carbocyclic or heterocyclic ring;

(vv) Ar represents a monocyclic or bicyclic aryl or heteroaryl ring, optionally substituted with between 1 and 3 substituents independently selected from halogen, C_{1-5} alkoxy, C_{1-5} alkyl, cyano, azido, nitro, $R^{22}R^{23}N$, $R^{24}SO_2$, $R^{24}OC=O$, $R^{25}R^{26}NC=O$, CF_3 , OCF_3 , CF_3S , and C_{1-5} alkylthio; R^{22} is hydrogen, C_{1-5} alkyl, phenyl, benzyl, phenethyl, C_{1-5} heterocyclyl, C_{2-8} acyl, aroyl, $R^{24}OC=O$, $R^{25}R^{26}NC=O$, $R^{24}SO$, $R^{24}SO_2$, or $R^{25}R^{26}NSO_2$; R^{23} is hydrogen or C_{1-5} alkyl;

(ww) alternatively, R^{22} and R^{23} can be taken together to form an optionally substituted 4- to 7- membered heterocyclic ring; R^{24} is hydrogen or C_{1-5} alkyl; R^{25} and R^{26} are independently hydrogen or C_{1-5} alkyl; or, alternatively, R^{25} and R^{26} can be taken together to form an optionally substituted 4- to 7- membered heterocyclic; W is NR^{27} or CHR^{28} ; R^{27} is hydrogen, C_{1-5} alkyl, $R^{29}OC=O$, $R^{30}R^{31}NC=O$, $R^{29}SO$, $R^{29}SO_2$, or $R^{30}R^{31}NSO_2$; or, alternatively, R^{27} and R^1 can be taken together to form an optionally substituted 5- or 6- membered heterocyclic ring, which ring may be saturated, unsaturated or aromatic; R^{28} is hydrogen, hydroxy, C_{1-5} heterocyclyl, phenyl, or C_{1-5} alkyl; R^{29} is C_{1-5} alkyl; R^{30} and R^{31} are independently selected from hydrogen, C_{1-5} alkyl; alternatively, R^{30} and R^{31} can be taken together to form an optionally substituted 4- to 7-membered heterocyclic;

(xx) one of R^5 and R^6 is H; R^7 and R^8 are taken together to form an optionally substituted 6- membered carbocyclic or heterocyclic ring; and Ar represents a monocyclic ring, optionally substituted with 1 to 2 substituents selected from halogen, C_{1-5} alkyl, cyano, azido, nitro, $R^{22}R^{23}N$, CF_3 and OCF_3 ;

(yy) both R^5 and R^6 are each H, and Ar is a six membered ring substituted with between 1 and 2 substituents independently selected from halogen, methyl,

CF₃, and OCF₃, said substituent or substituents being at the 4-position, or at the 3- and 4-positions;

(zz) a R⁷ and R⁸ taken together form tetrahydropyridinyl, optionally N-substituted with -(C=O)R⁴, -SO₂R⁴, or -(C=O)NHR⁴⁴;

5 (aaa) X_f is C=O, SO₂, or CHR^{1f}, and Y_f is O or NR^{2f}, where R^{2f} is H, C₁₋₅ alkyl, C₂₋₅ heterocyclyl, C₁₋₅ cyanoalkyl, or (C₁₋₅ alkoxy carbonyl)C₁₋₅ alkylene;

(bbb) R^{2f} is H, C₁₋₃ alkyl, or a C₂₋₅ heterocyclyl;

(ccc) X_f is C=O, and Y_f is O, CHR^{2f} or NR^{2f}, where R^{2f} is H, C₁₋₅ alkyl, C₂₋₅ heterocyclyl, C₁₋₅ cyanoalkyl, or (C₁₋₅ alkoxy carbonyl)C₁₋₅ alkylene;

10 (ddd) X_f is C=O and Y_f is O;

(eee) m is 0 and p is 0; m is 0 and p is 1; or m is 1 and p is 0;

(fff) p is 0;

(ggg) R^z is H;

(hhh) R^z is OH;

15 (iii) R^z is absent;

(jjj) R²⁰ and R³ taken together are a six-membered carbocyclic or heterocyclic ring optionally substituted with between 1 and 3 substituents independently selected from halo, C₁₋₃ alkoxy, di(C₁₋₃ alkyl)amino, and C₂₋₅ acyl;

(kkk) each of R²⁰ and R³ is H; and

20 (III) combinations of the above.

Specific preferred compounds include those in the Examples provided, such as:

1-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one ; 1-(1-{3-[3-(3,4-Dichloro-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one ; 3-(3,4-Dichloro-phenyl)-1-{3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide ; 6-Chloro-1-(1-{3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one ; 3-(3,4-Dichloro-phenyl)-1-{3-[4-(3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-

- piperidin-1-yl]-propyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide ; [3-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-acetonitrile ; [3-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-acetic acid ethyl ester ; 5-Chloro-3-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-benzoimidazol-2-one ; 1-{3-[4-(6-Chloro-3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(3,4-dichloro-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide ; 3-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,5-dimethyl-1,3-dihydro-benzoimidazol-2-one ; 3-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one ; 3-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-methoxy-1,3-dihydro-imidazo[4,5-b]pyridin-2-one ; 3-(4-Bromo-phenyl)-1-{2-hydroxy-3-[4-(5-methoxy-2-oxo-1,2-dihydro-imidazo[4,5-b]pyridin-3-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide ; 3-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-methoxy-1-methyl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one ; 5-Dimethylamino-3-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one ; 6-Chloro-1-(1-{3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one ; 1-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one ; 4-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-benzo[1,4]oxazin-3-one ; 4-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-

trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl)-piperidin-4-yl)-4H-benzo[1,4]oxazin-3-one ; and 1-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinazolin-2-one .

5

Furthermore, preferred compounds include those wherein Ar or Ar₁ is selected from 4-trifluoromethylphenyl, 4-bromophenyl, 4-chlorophenyl, 4-chloro-3-methylphenyl and 3,4-dichlorophenyl.

More preferred compounds include Examples 37 and 50.

10

Related Compounds

The invention provides the disclosed compounds and closely related, pharmaceutically acceptable forms of the disclosed compounds, such as salts, esters, amides, acids, hydrates or solvated forms thereof; masked or protected forms; and racemic mixtures, or enantiomerically or optically pure forms. Related compounds also include compounds of the invention that have been modified to be detectable, e.g., isotopically labelled with ¹⁸F for use as a probe in positron emission tomography (PET) or single-photon emission computed tomography (SPECT).

20

The invention also includes disclosed compounds having one or more functional groups (e.g., hydroxyl, amino, or carboxyl) masked by a protecting group. See, e.g., Greene and Wuts, Protective Groups in Organic Synthesis, 3rd ed., (1999) John Wiley & Sons, NY. Some of these masked or protected compounds are pharmaceutically acceptable; others will be useful as intermediates. Synthetic intermediates and processes disclosed herein, and minor modifications thereof, are also within the scope of the invention.

25

HYDROXYL PROTECTING GROUPS

Protection for the hydroxyl group includes methyl ethers, substituted
 5 methyl ethers, substituted ethyl ethers, substitute benzyl ethers, and silyl
 ethers.

Substituted Methyl Ethers

Examples of substituted methyl ethers include methoxymethyl,
 methylthiomethyl, *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl,
 10 benzyloxymethyl, *p*-methoxybenzyloxymethyl, (4-methoxyphenoxy)methyl,
 guaiacolmethyl, *t*-butoxymethyl, 4-pentenylloxymethyl, siloxymethyl, 2-
 methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl,
 2-(trimethylsilyl)ethoxymethyl, tetrahydropyranyl, 3-bromotetrahydropyranyl,
 tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-
 15 methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxido, 1-
 [(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl,
 tetrahydrofuranyl, tetrahydrothiofuranyl and 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-
 trimethyl-4,7-methanobenzofuran-2-yl.

20 Substituted Ethyl Ethers

Examples of substituted ethyl ethers include 1-ethoxyethyl, 1-(2-
 chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-
 methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-
 (phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-
 25 dinitrophenyl, and benzyl.

Substituted Benzyl Ethers

Examples of substituted benzyl ethers include *p*-methoxybenzyl, 3,4-
 dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-
 30 dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2- and 4-picolyl, 3-methyl-2-
 picolyl N-oxido, diphenylmethyl, *p*, *p'*-dinitrobenzhydryl, 5-dibenzosuberyl,

- triphenylmethyl, α -naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyldiphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 3-(1-midazol-1-ylmethyl)bis(4',4''-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, and benzisothiazolyl S,S-dioxido.

Silyl Ethers

- Examples of silyl ethers include trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, and *t*-butylmethoxyphenylsilyl.

Esters

- In addition to ethers, a hydroxyl group may be protected as an ester. Examples of esters include formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, *p*-*P*-phenylacetate, 3-phenylpropionate, 4-oxopentanoate(levulinate), 4,4-(ethylenedithio)pentanoate, pivaloate, adamantate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate(mesitoate)

Carbonates

- Examples of carbonate protecting groups include methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, 2-(triphenylphosphonio)ethyl, isobutyl, vinyl, allyl, *p*-nitrophenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, S-benzyl thiocarbonate, 4-ethoxy-1-naphthyl, and methyl dithiocarbonate.

Assisted Cleavage

- Examples of assisted cleavage include 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-
- 5 formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl carbonate, 4-(methylthiomethoxy)butyrate, and 2-(methylthiomethoxymethyl)benzoate.

Miscellaneous Esters

- 10 Examples of miscellaneous esters include 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (E)-2-methyl-2-
- 15 butenoate(tigloate), *o*-(methoxycarbonyl)benzoate, *p*-P-benzoate, α -naphthoate, nitrate, alkyl N,N,N',N'-tetramethylphosphorodiamidate, N-phenylcarbamate, borate, dimethylphosphinothioyl, and 2,4-dinitrophenylsulfenate.

Sulfonates

- 20 Examples of sulfonates include sulfate, methanesulfonate(mesylate), benzylsulfonate, and tosylate.

25 AMINO PROTECTING GROUPS

Protection for the amino group includes carbamates, amides, and special –NH protective groups.

- 30 Examples of carbamates include methyl and ethyl carbamates, substituted ethyl carbamates, assisted cleavage carbamates, photolytic cleavage carbamates, urea-type derivatives, and miscellaneous carbamates.

Carbamates

Examples of methyl and ethyl carbamates include methyl and ethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, and 4-methoxyphenacyl.

Substituted Ethyl

Examples of substituted ethyl carbamates include 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'- and 4'-pyridyl)ethyl, 2-(*N,N*-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, *N*-hydroxypiperidinyl, alkylidithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl and diphenylmethyl.

20 Assisted Cleavage

Examples of assisted cleavage include 2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-chloro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, and 2-(trifluoromethyl)-6-chromonylmethyl.

Photolytic Cleavage

Examples of photolytic cleavage include *m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, and phenyl(*o*-nitrophenyl)methyl.

Urea-Type Derivatives

Examples of urea-type derivatives include phenothiazinyl-(10)-carbonyl derivative, N' -*p*-toluenesulfonylaminocarbonyl, and N'-
 5 phenylaminothiocarbonyl.

Miscellaneous Carbamates

Examples of miscellaneous carbamates include *t*-amyl, S-benzyl
 10 thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(N,N-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(N,N-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-iodoethyl, isobornyl, isobutyl, isonicotinyl, *p*-(*p*'-
 15 methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium)benzyl, and 2,4,6-trimethylbenzyl.

20 Examples of amides include:

Amides

N-formyl, N-acetyl, N-chloroacetyl, N-trichloroacetyl, N-trifluoroacetyl, N-
 25 phenylacetyl, N-3-phenylpropionyl, N-picolinoyl, N-3-pyridylcarboxamide, N-benzoylphenylalanyl derivative, N-benzoyl, N-*p*-phenylbenzoyl.

Assisted Cleavage

N-*o*-nitrophenylacetyl, N-*o*-nitrophenoxyacetyl, N-acetoacetyl, (N'-
 30 dithiobenzoyloxycarbonylamino)acetyl, N-3-(*p*-hydroxyphenyl)propionyl, N-3-(*o*-nitrophenyl)propionyl, N-2-methyl-2-(*o*-nitrophenoxy)propionyl, N-2-methyl-2-(*o*-phenylazophenoxy)propionyl, N-4-chlorobutyryl, N-3-methyl-3-nitrobutyryl, N-*o*-nitrocinnamoyl, N-acetylmethionine derivative, N-*o*-nitrobenzoyl, N-*o*-(benzoyloxymethyl)benzoyl, and 4,5-diphenyl-3-oxazolin-2-one.

Cyclic Imide Derivatives

- 5 N-phthalimide, N-dithiasuccinoyl, N-2,3-diphenylmaleoyl, N-2,5-dimethylpyrrolyl, N-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, and 1-substituted 3,5-dinitro-4-pyridonyl.

10

SPECIAL – NH PROTECTIVE GROUPS

Examples of special NH protective groups include

- 15 N-Alkyl and N-Aryl Amines

- N-methyl, N-allyl, N-[2-(trimethylsilyl)ethoxy]methyl, N-3-acetoxypentyl, N-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), quaternary ammonium salts, N-benzyl, N-di(4-methoxyphenyl)methyl, N-5-dibenzosuberonyl, N-triphenylmethyl, 20 N-(4-methoxyphenyl)diphenylmethyl, N-9-phenylfluorenyl, N-2,7-dichloro-9-fluorenylmethylene, N-ferrocenylmethyl, and N-2-picolylamine N'-oxide.

Imine Derivatives

- 25 N-1,1-dimethylthiomethylene, N-benzylidene, N-*p*-methoxybenzylidene, N-diphenylmethylene, N-[(2-pyridyl)mesityl]methylene, and N-(N',N'-dimethylaminomethylene).

- 30 PROTECTION FOR THE CARBONYL GROUP

Acyclic Acetals and Ketals

Examples of acyclic acetals and ketals include dimethyl, bis(2,2,2-trichloroethyl), dibenzyl, bis(2-nitrobenzyl) and diacetyl.

35

Cyclic Acetals and Ketals

Examples of cyclic acetals and ketals include 1,3-dioxanes, 5-methylene-1,3-dioxane, 5,5-dibromo-1,3-dioxane, 5-(2-pyridyl)-1,3-dioxane, 1,3-dioxolanes, 4-bromomethyl-1,3-dioxolane, 4-(3-butenyl)-1,3-dioxolane, 4-phenyl-1,3-dioxolane, 4-(2-nitrophenyl)-1,3-dioxolane, 4,5-dimethoxymethyl-1,3-dioxolane, O,O'-phenylenedioxy and 1,5-dihydro-3H-2,4-benzodioxepin.

Acyclic Dithio Acetals and Ketals

Examples of acyclic dithio acetals and ketals include S,S'-dimethyl, S,S'-diethyl, S,S'-dipropyl, S,S'-dibutyl, S,S'-dipentyl, S,S'-diphenyl, S,S'-dibenzyl and S,S'-diacetyl.

Cyclic Dithio Acetals and Ketals

Examples of cyclic dithio acetals and ketals include 1,3-dithiane, 1,3-dithiolane and 1,5-dihydro-3H-2,4-benzodithiepin.

Acyclic Monothio Acetals and Ketals

Examples of acyclic monothio acetals and ketals include O-trimethylsilyl-S-alkyl, O-methyl-S-alkyl or -S-phenyl and O-methyl-S-2-(methylthio)ethyl.

Cyclic Monothio Acetals and Ketals

Examples of cyclic monothio acetals and ketals include 1,3-oxathiolanes.

MISCELLANEOUS DERIVATIVES

O-Substituted Cyanohydrins

Examples of O-substituted cyanohydrins include O-acetyl, O-trimethylsilyl, O-1-ethoxyethyl and O-tetrahydropyranyl.

Substituted Hydrazones

Examples of substituted hydrazones include N,N-dimethyl and 2,4-dinitrophenyl.

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Oxime Derivatives

Examples of oxime derivatives include O-methyl, O-benzyl and O-phenylthiomethyl.

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Imines

Substituted Methylene Derivatives, Cyclic Derivatives

15

Examples of substituted methylene and cyclic derivatives include oxazolidines, 1-methyl-2-(1'-hydroxyalkyl)imidazoles, N,N'-dimethylimidazolidines, 2,3-dihydro-1,3-benzothiazoles, diethylamine adducts, and methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide)(MAD)complex.

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PROTECTION FOR THE CARBOXYL GROUP

Esters

5 Substituted Methyl Esters

Examples of substituted methyl esters include 9-fluorenylmethyl, methoxymethyl, methylthiomethyl, tetrahydropyranyl, tetrahydrofuranyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, phenacyl, *p*-bromophenacyl, α -methylphenacyl, *p*-methoxyphenacyl, carboxamidomethyl, and N-phthalimidomethyl.

2-Substituted Ethyl Esters

Examples of 2-substituted ethyl esters include 2,2,2-trichloroethyl, 2-haloethyl, ω -chloroalkyl, 2-(trimethylsilyl)ethyl, 2-methylthioethyl, 1,3-dithianyl-2-methyl, 2-(*p*-nitrophenylsulfenyl)ethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(2'-pyridyl)ethyl, 2-(diphenylphosphino)ethyl, 1-methyl-1-phenylethyl, *t*-butyl, cyclopentyl, cyclohexyl, allyl, 3-buten-1-yl, 4-(trimethylsilyl)-2-buten-1-yl, cinnamyl, α -methylcinnamyl, phenyl, *p*-(methylmercapto)phenyl and benzyl.

Substituted Benzyl Esters

Examples of substituted benzyl esters include triphenylmethyl, diphenylmethyl, bis(*o*-nitrophenyl)methyl, 9-anthrylmethyl, 2-(9,10-dioxo)anthrylmethyl, 5-dibenzosuberyl, 1-pyrenylmethyl, 2-(trifluoromethyl)-6-chromylmethyl, 2,4,6-trimethylbenzyl, *p*-bromobenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, 4-(methylsulfinyl)benzyl, 4-sulfobenzyl, piperonyl, 4-picolyl and *p*-P-benzyl.

Silyl Esters

Examples of silyl esters include trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, *i*-propyldimethylsilyl, phenyldimethylsilyl and di-*t*-butylmethylsilyl.

Activated Esters

Examples of activated esters include thiols.

5

Miscellaneous Derivatives

Examples of miscellaneous derivatives include oxazoles, 2-alkyl-1,3-oxazolines, 4-alkyl-5-oxo-1,3-oxazolidines, 5-alkyl-4-oxo-1,3-dioxolanes, ortho esters, phenyl group and pentaaminocobalt(III) complex.

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Stannyl Esters

Examples of stannyl esters include triethylstannyl and tri-*n*-butylstannyl.

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AMIDES AND HYDRAZIDES

Amides

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Examples of amides include N,N-dimethyl, pyrrolidinyl, piperidinyl, 5,6-dihydrophenanthridinyl, *o*-nitroanilides, N-7-nitroindolyl, N-8-Nitro-1,2,3,4-tetrahydroquinolyl, and *p*-P-benzenesulfonamides.

Hydrazides

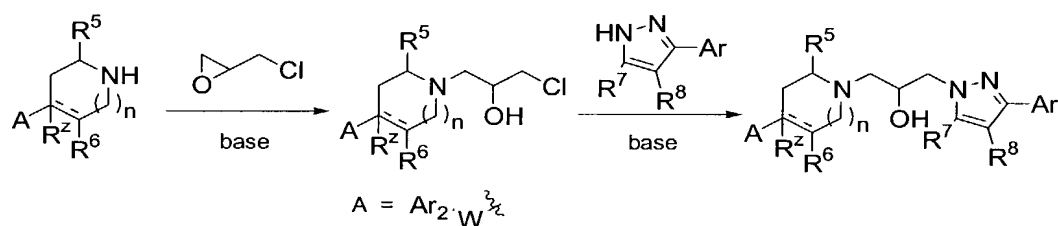
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Examples of hydrazides include N-phenyl and N,N'-diisopropyl hydrazides.

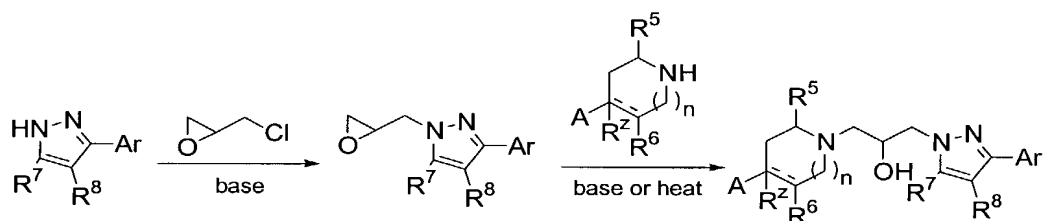
C. Synthesis

- The compounds of the present invention may be prepared by
- 5 conventional synthetic organic chemistry and by matrix or combinatorial methods according to Schemes 1 to 10 below, and Examples 1 to 31. Those of ordinary skill in the art will be able to modify and adapt the guidance provided herein to make the disclosed compounds.

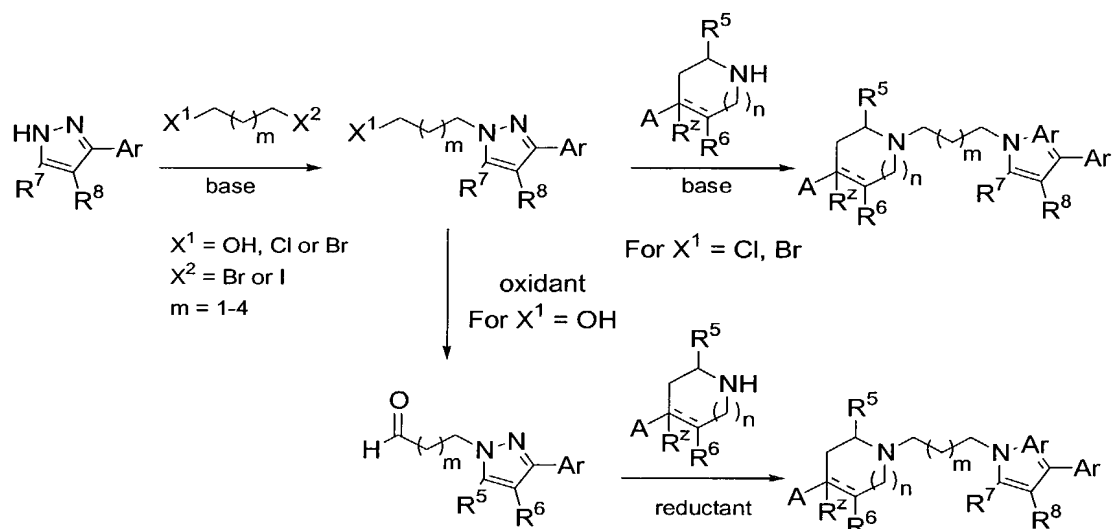
10 Scheme 1



15 Scheme 2

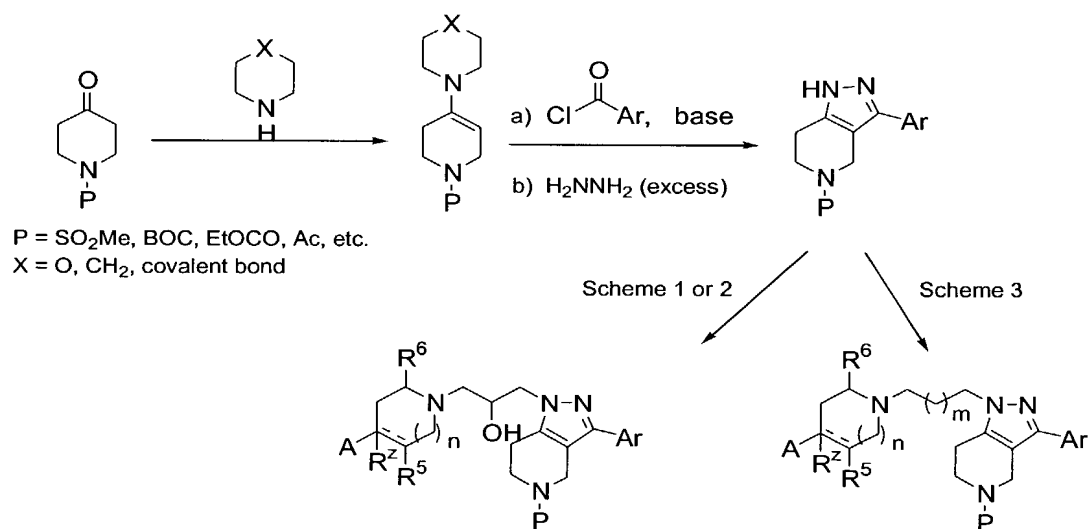


Scheme 3



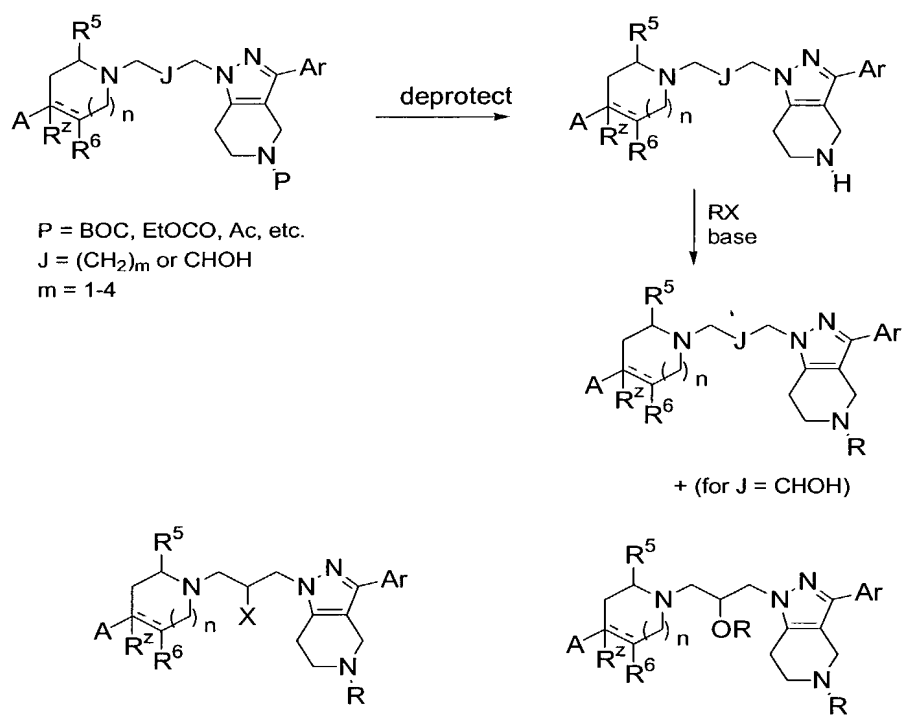
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Scheme 4



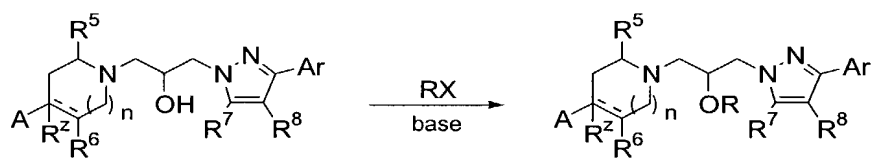
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Scheme 5



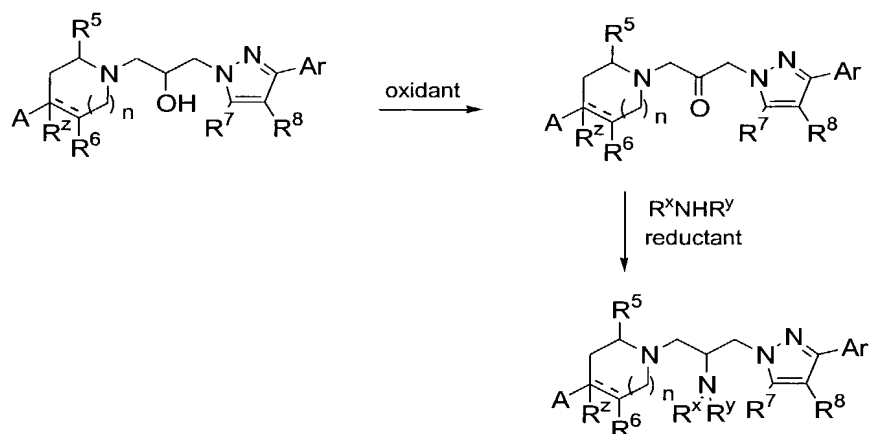
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Scheme 6



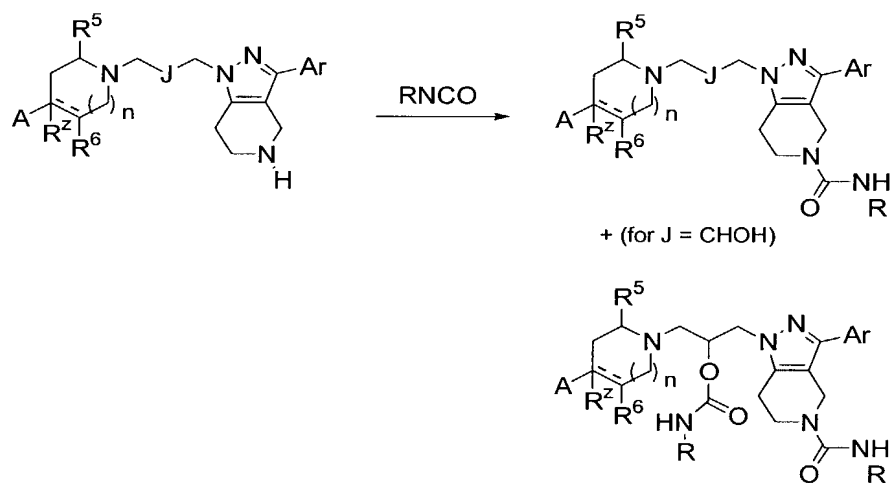
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Scheme 7



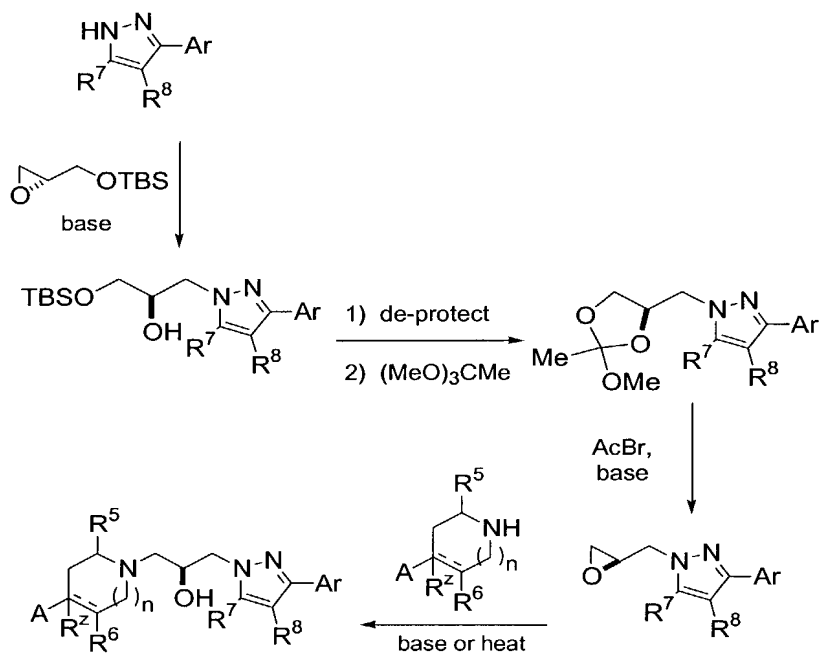
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Scheme 8



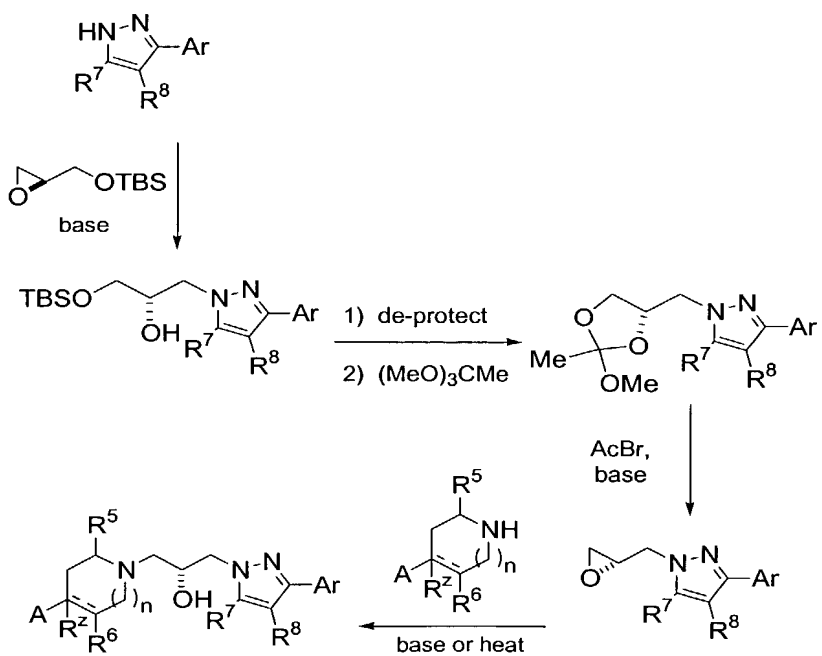
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Scheme 9



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Scheme 10



D. Formulation and Administration

5 The present compounds inhibit the proteolytic activity of human cathepsin S and therefore are useful as a medicine especially in methods for treating patients suffering from disorders or conditions which are modulated or regulated by the inhibition of cathepsin S activity.

10 The invention features a method for treating a subject with a condition mediated by cathepsin S, said method comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a compound of the invention. The invention also provides a method for inhibiting cathepsin S activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of a
15 pharmaceutical composition comprising a compound of the invention. A third method is a method for treating an autoimmune disease, or inhibiting the progression of an autoimmune disease, in a subject, said method comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a disclosed compound. The
20 autoimmune disease can be, for example, lupus, rheumatoid arthritis, or preferably, asthma. The invention also provides a method for treating or inhibiting the progression of tissue transplant rejection in a subject, the method comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a compound of the invention. The
25 administration step can occur before, during, and/or after a tissue transplant procedure.

In view of their inhibitory effect on the proteolytic activity of human cathepsin S the compounds of the present invention may be formulated into
30 various pharmaceutical forms for administration purposes. To prepare these pharmaceutical compositions, an effective amount of a particular compound, in base or acid addition salt form, as the active ingredient is intimately mixed with a pharmaceutically acceptable carrier.

A carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for oral administration or parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. These include water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. In view of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are generally employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Such additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of the compounds of formula I, due to their increased water solubility over the corresponding base form, are more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification herein refers to physically discrete units suitable as unitary dosages, each unit

containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Pharmaceutically acceptable acid addition salts include the therapeutically active non-toxic acid addition salt forms which the disclosed compounds are able to form. The latter can conveniently be obtained by treating the base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, palmoic and the like acids. The term addition salt also comprises the solvates which the disclosed compounds, as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like. Conversely the salt form can be converted by treatment with alkali into the free base form.

Stereoisomeric form defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the (R)- or (S)-configuration; substituents on bivalent cyclic saturated radicals may have either the cis- or trans-configuration. The invention encompasses stereochemically isomeric forms including diastereoisomers, as well as mixtures thereof in any proportion of the disclosed compounds. The disclosed compounds may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above

and following formulae are intended to be included within the scope of the present invention.

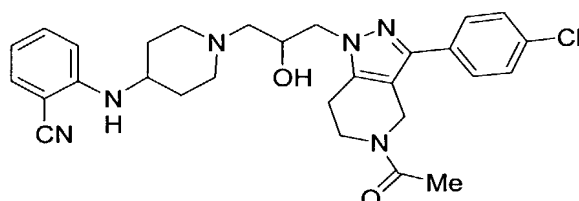
Those of skill in the treatment of disorders or conditions mediated by the cathepsin S enzyme could easily determine the effective daily amount from the test results presented hereinafter and other information. In general it is contemplated that a therapeutically effective dose would be from 0.001 mg/kg to 5 mg/kg body weight, more preferably from 0.01 mg/kg to 0.5 mg/kg body weight. It may be appropriate to administer the therapeutically effective dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 0.05 mg to 250 mg, and in particular 0.5 to 50 mg of active ingredient per unit dosage form. Examples include 2 mg, 4 mg, 7 mg, 10 mg, 15 mg, 25 mg, and 35 mg dosage forms. Compounds of the invention may also be prepared in time-release or subcutaneous or transdermal patch formulations. Disclosed compound may also be formulated as a spray or other topical or inhalable formulations.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the patient may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated patient and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned herein are therefore only guidelines.

The next section includes detailed information relating to the preparation, characterization, and use of the disclosed compounds.

E. Examples

EXAMPLE 1



2-(1-{3-[5-Acetyl-3-(4-chloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-ylamino)-benzonitrile.

A. 1-[3-(4-Chloro-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

To a stirred solution of 50 g (0.35 mol) of *N*-acetyl-4-piperidone and 31 g (0.35 mol) of morpholine in benzene (350 mL) was added a catalytic amount (~ 0.25 g) of *p*-toluenesulfonic acid. The mixture was heated to reflux for 10 h with a Dean-Stark trap. The solvent was removed under reduced pressure to give a brown oil. The crude product was diluted with CH₂Cl₂ (175 mL) and 50.0 mL (0.35 mol) of Et₃N was added. The mixture was cooled to 0 °C and a solution of 45.0 mL (0.35 mol) of 4-chlorobenzoyl chloride in CH₂Cl₂ (50 mL) was added slowly by dropping funnel over 1 h. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was then diluted with 1 *N* HCl (150 mL) and stirred vigorously for 3 h. The aqueous layer was extracted with CH₂Cl₂ (3 x 250 mL) and the combined extracts were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude oil was diluted with EtOH (350 mL) and cooled to 0 °C. To this stirred solution was slowly added 33.0 mL (1.06 mol) of hydrazine and the mixture was allowed to warm to room temperature and stir overnight during which time a white precipitate formed. The volume of the reaction was reduced to ~150 mL and EtOAc (750 mL) was added to the mixture. The suspension was stirred vigorously for 2 h and was filtered then washed with EtOAc (2 x 200 mL) and dried under

vacuum to afford 41.4 g (42% over 3 steps) of a pale yellow solid. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.3. MS (electrospray): *m/z* calculated for C₁₄H₁₄ClN₃O [M+H]⁺ 276.08, observed 276.0. ¹H NMR (400 MHz, CDCl₃, a mixture of amide rotamers): 7.65 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 9.3 Hz, 2H), 7.58 (d, *J* = 10.5 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 4.94 (s, 2H), 4.78 (s, 2H), 4.08 (t, *J* = 5.9 Hz, 2H), 3.90 (t, *J* = 5.8 Hz, 2H), 3.02 (t, *J* = 5.8 Hz, 2H), 2.96 (t, *J* = 5.9 Hz, 2H), 2.36 (s, 3H), 2.31 (s, 3H).

B. 1-[3-(4-Chloro-phenyl)-1-oxiranylmethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

To a stirred solution of 1.00 g (3.63 mmol) of 1-[3-(4-chloro-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone and 2.85 mL (36.3 mmol) of epichlorohydrin was added 1.30 g (3.99 mmol) of solid Cs₂CO₃. The reaction was stirred for 48 h and the solvent was removed under reduced pressure.

The residue was then diluted with H₂O (50 mL) and EtOAc (50 mL). The layers were separated, and the organic layer was washed with H₂O (25 mL) and brine (25 mL), dried over Na₂SO₄ and the solvent was removed under reduced pressure. Purification by flash chromatography (silica, 0-15% acetone/CH₂Cl₂) afforded 0.72 g (60%) of a white solid. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.5. MS (electrospray): *m/z* calculated for C₁₇H₁₈ClN₃O₂ [M+H]⁺, 332.11, observed 332.0. ¹H NMR (400 MHz, CDCl₃, a mixture of amide rotamers): 7.60 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 4.80 and 4.73 (A and B of AB quartet, *J*_{ab} = 15.8 Hz, 2H), 4.60 (s, 2H), 4.47 (dd, *J* = 15.3, 2.5 Hz, 1H), 4.42 (dd, *J* = 15.0, 2.7 Hz, 1H), 4.11 (dd, *J* = 5.3, 2.5 Hz, 1H), 4.08 (dd, *J* = 5.1, 3.3 Hz, 1H), 3.99-3.85 (m, 2H), 3.73 (dt, *J* = 5.9, 1.8 Hz, 2H), 3.37 (m, 2H), 2.87-2.80 (m, 3H), 2.80-2.69 (m, 3H), 2.53 (dd, *J* = 4.7, 2.5 Hz, 1H), 2.48 (dd, *J* = 4.6, 2.6, 1H), 2.19 (s, 3H), 2.15 (s, 3H).

C. 1-{3-(4-Chloro-phenyl)-1-[3-(1,4-dioxo-8-aza-spiro[4.5]dec-8-yl)-2-hydroxy-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl}-ethanone.

To a stirred solution of 3.20 g (9.64 mmol) of 1-[3-(4-chloro-phenyl)-1-oxiranylmethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone and 2.07 g (14.5 mmol) of 1,4-dioxo-8-azaspiro[4.5]decane in CH₂Cl₂ (65 mL) was

added 1.79 g (2.89 mmol) of $\text{Yb}(\text{OTf})_3 \cdot \text{H}_2\text{O}$. The reaction was stirred overnight and was then directly purified by flash chromatography (silica, 0-5% MeOH/ CH_2Cl_2) to afford 3.70 g (81%) of the title compound. TLC (silica, 5% MeOH/ CH_2Cl_2): R_f = 0.35. MS (electrospray), m/z calculated for $\text{C}_{24}\text{H}_{31}\text{ClN}_4\text{O}_4$ $[\text{M}^+ + \text{H}]$, 475.20, observed 475.1.

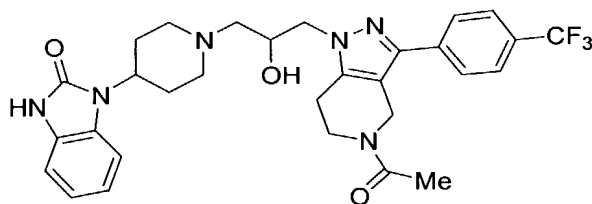
D. 1-{3-[5-Acetyl-3-(4-chloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-one.

A suspension of 0.50 g (0.96 mmol) of 1-{3-(4-chloro-phenyl)-1-[3-(1,4-dioxo-8-aza-spiro[4.5]dec-8-yl)-2-hydroxy-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl}-ethanone in 1 N HCl (2.0 mL) was heated to 65 °C for 48 h in a sealed vessel. The reaction was allowed to cool to room temperature and was diluted with CHCl_3 (20 mL) and saturated NaHCO_3 (20 mL). The aqueous phase was extracted with CHCl_3 (2 x 10 mL) and the combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was then diluted with Ac_2O (3.0 mL) and was stirred for 48 h. The solvent was removed under reduced pressure and the crude material was pumped down overnight. The resulting solid was dissolved in MeOH (5.0 mL) and a catalytic amount (0.05 g) of K_2CO_3 was added to the mixture and stirring was continued overnight. The reaction was then diluted with H_2O (20 mL) and CH_2Cl_2 (20 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (silica, 0-10% MeOH/ CH_2Cl_2) afforded 0.29 g (65% over 3 steps) of a white solid. TLC (silica, 5% MeOH/ CH_2Cl_2): R_f = 0.35. MS (electrospray); m/z calculated for $\text{C}_{22}\text{H}_{27}\text{ClN}_4\text{O}_3$, $[\text{M} + \text{H}]^+$, 431.18, observed 431.1. ^1H NMR (400 MHz, CDCl_3 , a mixture of amide rotamers): 7.59 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 4.85 and 4.73 (A and B of AB quartet, J_{ab} = 15.8 Hz, 1H), 4.62 (s, 1H), 4.26-4.12 (m, 2H), 4.09-3.68 (m, 4H), 3.49 (s, 1.5H), 3.28 (s, 1.5H).

E. 2-(1-{3-[5-Acetyl-3-(4-chloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-ylamino)-benzonitrile.

To a stirred solution of 50.0 mg (116.0 μmol) of 5-1-{3-[5-acetyl-3-(4-chloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-one and 9.6 mg (82.5 μmol) of 2-aminobenzonitrile in AcOH (0.5 mL) was added 130.0 mg (917.0 μmol) Na_2SO_4 and the reaction was allowed to stir for 1 h. To this mixture was added 58.0 mg (275.0 μmol) $\text{NaBH}(\text{OAc})_3$ and the reaction was stirred for 48 h. The mixture was diluted with CH_2Cl_2 (20 mL) and saturated NaHCO_3 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (silica, 0-5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) afforded 9.0 mg (20%) of a white solid. TLC (silica, 5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$): R_f = 0.2. MS (electrospray): m/z calculated for $\text{C}_{29}\text{H}_{33}\text{ClN}_6\text{O}_2$, $[\text{M}+\text{H}]^+$, 533.24, observed 533.3. ^1H NMR (400 MHz, CDCl_3 , a mixture of amide rotamers): 7.58 (d, J = 8.6 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.43-7.34 (m, 4H), 6.69 (dt, J = 7.6, 4.0 Hz, 1H), 6.64 (d, J = 8.6 Hz, 1H), 4.83 and 4.73 (A and B of AB quartet, J_{ab} = 15.7 Hz, 1H), 4.61 (s, 1H), 4.44 (d, J = 7.3 Hz, 1H), 4.33-4.14 (m, 2H), 4.11-3.84 (m, 2H), 3.83-3.67 (m, 1H), 3.55-3.43 (m, 1H), 3.17-2.94 (m, 1H), 2.93-2.75 (m, 2H), 2.74-2.54 (m, 2H), 2.21 (s, 1.5H), 2.16 (s, 1.5H), 2.23-1.53 (m, 9H).

EXAMPLE 2



1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one.

A. 1-[3-(4-Trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

A solution of *N*-acetyl-4-piperidone (2.82 g, 20 mmol), morpholine (1.93 mL, 22 mmol) and *p*-toluenesulfonic acid (5 mg) in benzene (8.5 mL) was refluxed for 8 h in a Dean-Stark apparatus. The solvent was removed and the residue dissolved in CH₂Cl₂ (20 mL). Triethylamine (3.1 mL) was added and *p*-trifluoromethylbenzoyl chloride (3.27 mL, 22 mmol) in CH₂Cl₂ (4 mL) was added dropwise into the solution at 0 °C. The reaction mixture was stirred at 25 °C for 24 h and diluted with aqueous HCl (5%, 25 mL). After stirring for another 30 min, the organic layer was separated, washed with H₂O (20 mL), dried (Na₂SO₄), and concentrated. The residue was dissolved in EtOH (95%, 18 mL) and treated at 0 °C with hydrazine (2.9 mL, 60 mmol). The mixture was stirred at 25 °C for 3 h and H₂O (4 mL) was added. Most of the volatiles were removed and the residue extracted with CH₂Cl₂ (50 mL). The organic layer was separated, washed with H₂O (20 mL), dried over Na₂SO₄, and concentrated. Column chromatography (silica, 5% MeOH/CH₂Cl₂) provided 5.1 g (83%) of a white powder. TLC (silica, 10% MeOH/CH₂Cl₂): R_f = 0.30. MS (electrospray): *m/z* 332.0 ([M+Na]⁺, C₁₅H₁₄F₃N₃O requires 309.1). ¹H NMR (CDCl₃, 400 MHz, a mixture of two rotamers): 7.73-7.67 (m, 4H), 4.85 (s, 1.2H), 4.68 (s, 0.8H), 3.96 (t, *J* = 4.5 Hz, 0.8H), 3.78 (t, *J* = 4.5 Hz, 1.2H), 2.89 (t, *J* = 4.5 Hz, 1.2H), 2.83 (t, *J* = 4.5 Hz, 0.8H), 2.23 (s, 1.8H), 2.18 (s, 1.2H).

B. 1-[1-Oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

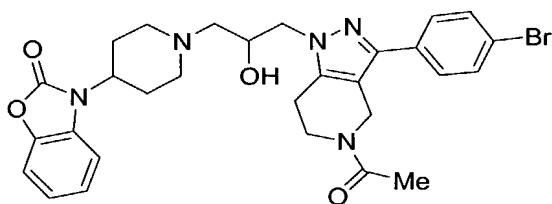
A solution of 1-[3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone (2.4 g, 7.77 mmol) in DMF (15 mL) was treated with cesium carbonate (5.05 g, 15.5 mmol) and epichlorohydrin (6.1 mL, 77.7 mmol) at 25 °C and stirred for 24 h before it was diluted with EtOAc (100 mL) and H₂O (50 mL). The organic layer was separated, washed with H₂O (2 x 50 mL), brine (50 mL), dried over Na₂SO₄, and concentrated. Column chromatography (silica, 10% acetone/CH₂Cl₂) provided 2.30 g (81%) of a white powder. TLC (silica, 10% MeOH/CH₂Cl₂): R_f = 0.35. MS (electrospray): *m/z* 388.0 ([M+Na]⁺,

$C_{18}H_{18}F_3N_3O_2$ requires 365.1). 1H NMR ($CDCl_3$, 400 MHz, a mixture of two rotamers): 7.77 and 7.63 (AB pattern, $J_{ab} = 8.2$ Hz, 2H), 7.71 and 7.67 (AB pattern, $J_{ab} = 8.4$ Hz, 2H), 4.82 and 4.76 (AB pattern, $J_{ab} = 15.5$ Hz, 1.2H), 4.58 (s, 0.8H), 4.45-4.35 (m, 1H), 4.08-4.02 (m, 1H), 3.92-3.80 (m, 1H), 3.70-3.63 (m, 1H), 3.30 (m, 1H), 2.80-2.67 (m, 3H), 2.48-2.42 (m, 1H), 2.13 (s, 1.3H), 2.08 (s, 1.7H).

C. 1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one.

A solution of 1-[1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone (1.17 g, 3.2 mmol) in DMF (10 mL) was treated with ytterbium(III) triflate (0.4 g, 0.64 mmol) and 4-(2-keto-1-benzimidazoliny)piperidine (1.04 g, 4.8 mmol) at 25 °C and stirred for 48 h before it was diluted with CH_2Cl_2 (100 mL) and H_2O (50 mL). The organic layer was separated, washed with H_2O (2 x 50 mL), dried over Na_2SO_4 , and concentrated. Flash column chromatography (silica, 5% MeOH/ CH_2Cl_2) afforded 1.71 g (92%) of a white powder. TLC (silica, 10% MeOH/ CH_2Cl_2): $R_f = 0.25$. MS (electrospray): m/z 583.5 ($[M+H]^+$, $C_{30}H_{33}F_3N_6O_3$ requires 582.3). 1H NMR ($CDCl_3$, 400 MHz, a mixture of two rotamers): 9.30 (br s, 0.5H), 9.25 (br s, 0.5H), 7.82 and 7.68 (AB pattern, $J_{ab} = 8.2$ Hz, 2H), 7.76 and 7.72 (AB pattern, $J_{ab} = 8.4$ Hz, 2H), 7.25-7.05 (m, 4H), 4.92 and 4.80 (AB pattern, $J_{ab} = 15.6$ Hz, 1.1H), 4.70 (s, 0.9H), 4.40-3.70 (m, 7H), 3.20-2.82 (m, 4H), 2.60-2.45 (m, 4H), 2.35-2.25 (m, 1H), 2.25 (s, 1.5H), 2.20 (s, 1.5H), 1.90-1.87 (m, 2H).

EXAMPLE 3



3-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3H-benzooxazol-2-one.

5 A. 1-[3-(4-Bromo-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

A flask equipped with a Dean-Stark trap, was charged with *N*-acetyl-4-piperidone (100.1 g, 709 mmol), piperidine (68 mL, 779 mmol), *p*TsOH (3.7 g) and benzene (500 mL). The mixture was heated to 125 °C. After 17 h the mixture was allowed to cool and divided into two portions. A solution of *p*-bromobenzoyl chloride (70.0 g, 319 mmol) in CH₂Cl₂ (400 mL) was added dropwise to a 0 °C solution of the enamine (ca. 355 mmol) in CH₂Cl₂ (320 mL) over 15 h. The mixture was then allowed to warm to 23 °C and stirred for an additional 5 h. The solution was treated with 1 *N* HCl (500 mL) and stirred vigorously for 1.5 h. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 300 mL). The combined extracts were washed with sat. aqueous NaHCO₃ (300 mL), H₂O (300 mL), brine (300 mL), dried over Na₂SO₄ and concentrated. The residue was dissolved in MeOH (300 mL) and treated with NH₂NH₂ (50.0 mL, 1.59 mol). The mixture was stirred for 17 h before the precipitate formed was collected by filtration and air dried to give 52 g (50%) of the title compound which was suitable for use without further purification. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.3. MS (electrospray): *m/z* calculated for C₁₄H₁₅⁷⁹BrN₃O [M+H]⁺, 320.04, found 320. ¹H NMR (CD₃OD/CDCl₃, 400 MHz, a mixture of amide rotamers): 7.53 and 7.35 (A and B of AA'BB', *J* = 8.5 Hz, 2H), 7.51 and 7.39 (A and B of AA'BB', *J* = 8.6 Hz, 2H), 4.72 (s, 2H), 4.58 (s, 2H), 3.85 (t, *J* = 5.9 Hz, 2H), 3.71 (t, *J* = 5.8 Hz, 2H), 2.81, (t, *J* = 5.8 Hz, 2H), 2.74, (t, *J* = 5.8 Hz, 2H), 2.16 (s, 3H), 2.11 (s, 3H).

30 B. 1-[3-(4-Bromo-phenyl)-1-oxiranylmethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

Cs₂CO₃ (11.58 g, 35.5 mmol) was added to a solution of 1-[3-(4-bromo-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone (7.59 g, 23.7 mmol) and epichlorohydrin (20 mL, 234 mmol) in DMF (100 mL). The mixture was

stirred for 18 h then diluted with EtOAc (800 mL) and washed with saturated aqueous NaHCO₃ (2 x 100 mL), H₂O (2 x 100 mL), and brine (100 mL). The NaHCO₃ layer was extracted with EtOAc (2 x 150 mL). The combined washes were extracted with EtOAc (2 x 100 mL). The combined extracts were dried
5 over Na₂SO₄ and concentrated. Column chromatography (silica, 10-20% acetone/CH₂Cl₂) afforded 4.98 g (56%) of the title compound. HPLC, *t*_R = 4.90 min. (Reverse phase conditions: HP 1100 LCMS, Phenomenex luna 2.1 x 150 mm column, 60% MeOH/ H₂O (0.5% AcOH) to 90% MeOH/ H₂O (0.5% AcOH), held at initial conditions for 2 min then ramped to final conditions over 5 min.)
10 MS (electrospray): *m/z* calculated for C₁₇H₁₉⁷⁹BrN₃O₂, [M+H]⁺, 376.07, found 376.0. ¹H NMR (CDCl₃, 400 MHz, a mixture of amide rotamers): 7.47 (d with fine splittings, *J* = 8.5, Hz, 2H), 7.44 (m, 4H), 7.38 (d with fine splittings, *J* = 8.5, Hz, 2H), 4.71 and 4.64 (A and B of AB quartet, *J*_{ab} = 15.7 Hz, 2H), 4.51 (s, 2H), 4.39 (dd, *J* = 15.1, 2.5 Hz, 1H), 4.34 (dd, *J* = 15.0, 2.9 Hz, 1H), 4.02 (dd, *J* =
15 5.2, 3.9 Hz, 1H), 3.98 (dd, *J* = 5.3, 3.7 Hz, 1H), 3.83 (m, 2H), 3.64 (m, 2H), 3.25 (br m, 2H), 2.80-2.60 (m, 6H), 2.46 (dd, *J* = 4.6, 2.6 Hz, 1H), 2.38 (dd, *J* = 4.6, 2.6 Hz, 1H), 2.10 (s, 3H), 2.06 (s, 3H).

C. 4-(2-Oxo-benzooxazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester.

20 To a stirred solution of 1.00 g (5.01 mmol) of *tert*-butyl 4-oxo-1-piperidinecarboxylate and 0.55 g (5.01 mmol) of 2-aminophenol in CH₂Cl₂ (15 mL) under nitrogen at rt was added 1.62 g (7.52 mmol) of NaBH(OAc)₃ in one portion and the mixture was stirred for 14 h. The mixture was diluted with CH₂Cl₂ (50 mL) and saturated NaHCO₃ (75 mL) and the layers were separated.
25 The aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, and the solvent was removed under reduced pressure. The crude solid was diluted with CH₂Cl₂ (15 mL) and 0.89 g (5.51 mmol) of carbonyldiimidazole was added in one portion and mixture was stirred for 16 h. The mixture was diluted with CH₂Cl₂ (50 mL)
30 and 1 N HCl (50 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, and the solvent was removed under reduced pressure. Flash chromatography (silica, 0-5% acetone/CH₂Cl₂)

afforded 1.59 g (99%) of a white solid. TLC (silica, 5% acetone/CH₂Cl₂): R_f = 0.6. MS (electrospray): *m/z* calculated for C₁₇H₂₂N₂O₄, [M+Na]⁺, 341.1, observed 341.1.

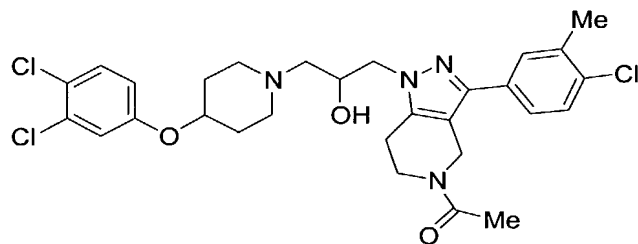
5 D. 3-Piperidin-4-yl-3H-benzooxazol-2-one.

To a stirred solution of 1.00 g (2.87 mmol) of 4-(2-oxo-benzooxazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester in CH₂Cl₂ (6.0 mL) was added TFA (6.0 mL) and the mixture was stirred for 12 h. The solvents were removed under reduced pressure and the crude solid was diluted in MeOH (10 mL) and
10 saturated NaHCO₃ (15 mL) was added to the mixture and stirring was continued for 10 min. The solution was diluted with CH₂Cl₂ (30 mL) and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL) and the organic layers were combined, dried over Na₂SO₄ and the solvent was removed under reduced pressure to afford 1.02 g (88%) of a pale yellow
15 solid. TLC (silica, 10% MeOH/CH₂Cl₂): R_f = 0.1. MS (electrospray): *m/z* calculated for C₁₂H₁₄N₂O₂, [M+H]⁺, 219.11, observed 219.1.

E. 3-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3H-benzooxazol-2-one.

20 To a stirred mixture of 0.025 g (0.066 mmol) of 3-piperidin-4-yl-3H-benzooxazol-2-one and 0.015 g (0.066 mmol) of 1-[3-(4-bromo-phenyl)-1-oxiranylmethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone in EtOH (0.5 mL) was added 0.01 mL (0.066 mmol) of Et₃N. The mixture was heated to 80 °C in a sealed vessel for 16 h. The reaction was cooled and the solvent
25 was removed under reduced pressure. Flash chromatography (silica, 0-5% MeOH/CH₂Cl₂) afforded 0.030 g (79%) of a white foam. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.4. MS (electrospray): *m/z* calculated for C₂₉H₃₂BrN₅O₄, [M+H]⁺, 594.16, observed 594.2. ¹H NMR (400 MHz, CDCl₃, a mixture of amide rotamers): 7.60-7.43 (m, 4H), 7.23-7.06 (m, 4H), 4.83 and 4.73 (A and B
30 of AB quartet, J_{ab} = 15.4 Hz, 1H), 4.61 (s, 1H), 4.38-3.66 (m, 7H), 3.37-3.02 (m, 2H), 2.99-2.28 (m, 6H), 2.21 (s, 1.5H), 2.16 (s, 1.5H), 1.99-1.83 (m, 3H).

EXAMPLE 4



1-(3-(4-Chloro-3-methyl-phenyl)-1-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone.

5

A. 1-[3-(4-Chloro-3-methyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

To a stirred solution of 1-acetyl-4-piperidone (3 g, 0.021 mol) and morpholine (1.86 g, 0.21 mol) in benzene (21 mL) was added a catalytic amount (~0.015 g) of *p*-toluenesulfonic acid. The mixture was heated to reflux for 10 h under a Dean-Stark trap. The solvent was removed under reduced pressure to give a brown oil. The crude product was diluted with CH₂Cl₂ (10.5 mL), and Et₃N (3.0 mL, 0.021 mol) was added. The mixture was cooled to 0 °C, and a solution of 3-methyl-4-chlorobenzoyl chloride (2.7 mL, 0.021 mol) in CH₂Cl₂ (3.0 mL) was added slowly by dropping funnel over 1 h. The mixture was allowed to warm to room temperature and stir overnight. The reaction mixture was then diluted with 1 *N* HCl (9.0 mL) and stirred vigorously for 3 h. The aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined extracts were dried over Na₂SO₄, and the solvent was removed under reduced pressure. The crude oil was diluted with EtOH (21 mL) and cooled to 0 °C. To this stirred solution was slowly added hydrazine (2.0 mL, 0.064 mol), and the mixture was allowed to warm to room temperature and stir overnight, during which time a white precipitate formed. The volume of the reaction mixture was reduced to ~9 mL, and EtOAc (45 mL) was added. The suspension was stirred vigorously for 2 h and was filtered then washed with EtOAc (2 x 12 mL) and dried under vacuum to afford 4.93 g (81% over 3 steps) of a pale yellow solid. TLC (silica, 10% acetone/CH₂Cl₂): R_f = 0.2. MS (electrospray): exact mass calculated for C₁₅H₁₆ClN₃O, 289.10; *m/z* found, 290.1 [M⁺+H].

B. 1-[3-(4-Chloro-3-methyl-phenyl)-1-oxiranylmethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

Cs₂CO₃ (11 g, 33.8 mmol) was added to a solution of 1-[3-(4-chloro-3-methyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone (4.9 g, 16.9 mmol) in DMF (49 mL), which was then stirred for 15 min. Epichlorohydrin (13.2 mL, 169 mmol) was added, and the mixture was stirred under N₂ at room temperature for 16 h. EtOAc (250 mL) was added to the reaction mixture, which was then stirred for 5 min. The resulting solution was washed with water (2 x 50 mL) and brine (1 x 50 mL). The organic extracts were dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (silica, 10-20% acetone/CH₂Cl₂) to obtain 3.8 g (65%) of a white solid. TLC (silica, 10% acetone/CH₂Cl₂): R_f = 0.3. MS (electrospray): exact mass calculated for C₁₈H₂₀ClN₃O₂, 345.12; *m/z* found, 346.1 [M⁺+H], 368.0 [M⁺+Na],

C. 4-(3,4-Dichlorophenoxy)-piperidinium trifluoroacetate.

A suspension of 0.69 g (20.0 mmol) of triphenylphosphine (polymer supported, 3 mmol P/g) in CH₂Cl₂ (4.0 mL) was stirred for 15 min to swell the resin. To this suspension was added 0.20 g (1.00 mmol) of 1-*tert*-butoxycarbonyl-4-piperidinol, 0.16 g (1.00 mmol) of 3,4-dichlorophenol, and 0.35 g (1.50 mmol) of di-*tert*-butyl azodicarboxylate. The reaction was stirred for 4 h and was filtered and the resin was washed with 5% MeOH/CH₂Cl₂ (2 x 20 mL) and Et₂O (20 mL). The organic layers were combined and the solvent was removed. The crude oil was diluted with CH₂Cl₂ (2.0 mL) and TFA (2.0 mL) and the mixture was stirred overnight. The solvent was removed under reduced pressure to afford the crude TFA salt which was used without further purification. TLC (silica, 10% MeOH/CH₂Cl₂): R_f = 0.1. MS (electrospray): *m/z* calculated for C₁₁H₁₃Cl₂NO, [M+H]⁺, 246.04, observed 246.1.

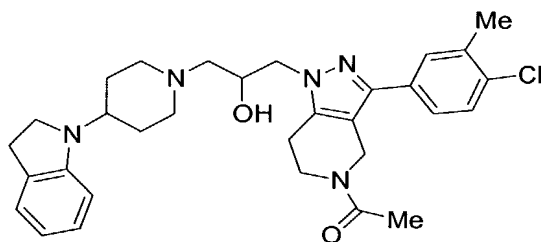
D. 1-(3-(4-Chloro-3-methyl-phenyl)-1-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone.

To a stirred solution of 25.0 mg (0.066 mmol) of 1-[3-(4-chloro-3-methyl-phenyl)-1-oxiranylmethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone and 25.0 mg (0.10 mmol) of 4-(3,4-dichlorophenoxy)-piperidinium trifluoroacetate in EtOH (0.5 mL) was added 0.019 mL (0.014 mmol) of Et₃N.

- 5 The mixture was heated to 80 °C in a sealed vessel for 16 h. The reaction was cooled and the solvent was removed under reduced pressure. Flash chromatography (0-5% MeOH/CH₂Cl₂) afforded 28 mg (74%) of a pale yellow foam. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.5. MS (electrospray): *m/z* calculated for C₂₉H₃₃Cl₃N₄O₃, [M+H]⁺, 591.16, observed 591.2. ¹H NMR (400
- 10 MHz, CDCl₃, a mixture of amide rotamers): 7.51 (d, *J* = 6.9 Hz, 1H), 7.41-7.29 (m, 3H), 6.99 (d, *J* = 2.9 Hz, 1H), 6.74 (dd, *J* = 9.0, 3.1 Hz, 1H), 4.82 and 4.73 (A and B of AB quartet, *J*_{ab} = 15.7 Hz, 1H), 4.60 (s, 1H), 4.46-3.93 (m, 4H), 3.92-3.83 (m, 1H), 3.82-3.68 (m, 1H), 3.08-2.51 (m, 6H), 2.43 (s, 1.5H), 2.41 (s, 1.5H), 2.21 (s, 1.5H), 2.15 (s, 1.5H) 2.00-1.83 (m, 3H), 1.75-1.39 (m, 4H).

15

EXAMPLE 5



- 20 1-(3-(4-Chloro-3-methyl-phenyl)-1-{3-[4-(2,3-dihydro-indol-1-yl)-piperidin-1-yl]-2-hydroxy-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone.

A. 1-Piperidin-4-yl-2,3-dihydro-1H-indole.

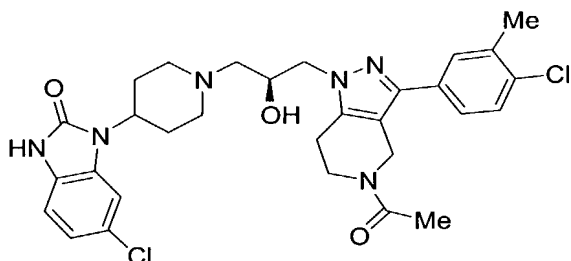
- 25 Indoline (11.0 g, 92 mmol) and *N*-BOC-4-piperidone (18.4 g, 92 mmol) were set stirring in 300 mL of CH₂Cl₂ under an atmosphere of nitrogen at rt. Acetic acid (5.5 mL, 96 mmol) was then added. After 1.5 h sodium triacetoxymethylborohydride (27.4 g, 129 mmol) was added and the mixture was left stirring for 4 days. The mixture was quenched by the slow addition of

saturated NaHCO_3 . The organics were separated, dried (MgSO_4) and the solvent was evaporated under reduced pressure to give 28 g (100%) of a clear dark green liquid. The crude material was brought up in 1:1 TFA/ CH_2Cl_2 (100 mL) and stirred at room temperature. After 45 min the solvent was evaporated under reduced pressure, the oil brought up in EtOAc, and cooled on ice to form a beige precipitate. The solid was filtered, washed with Et_2O and air dried to give 22.5 g (57%) of a white solid as a TFA salt. MS (electrospray): exact mass calculated for $\text{C}_{13}\text{H}_{18}\text{N}_2$, 202.15; m/z found, 203.2. ^1H NMR (400MHz, $\text{DMSO}-d_6$): 8.74 (br s, 1H), 8.46 (br s, 1H), 7.07 (m, 2H), 6.63 (m, 2H), 3.81 (br s, 1H), 3.46 (m, 2H), 3.37 (m, 2H), 3.12 (m, 2H), 2.95 (m, 2H), 1.86 (m, 4H).

B. 1-(3-(4-Chloro-3-methyl-phenyl)-1-{3-[4-(2,3-dihydro-indol-1-yl)-piperidin-1-yl]-2-hydroxy-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone.

1-Piperidin-4-yl-2,3-dihydro-1H-indole (TFA salt) (506 mg, 1.18 mmol) and 1-[3-(4-chloro-3-methyl-phenyl)-1-oxiranylmethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone (261 mg, 0.75 mmol) were set stirring in 20 mL of EtOH and heated to 80 °C. After 20 h the mixture was cooled, evaporated, brought up in EtOAc and washed with saturated NaHCO_3 . The organics were dried (MgSO_4) and evaporated to give a clear golden oil. Flash chromatography (silica, 100% acetone) gave 260 mg (63%) of a white solid. TLC (silica, 100% acetone): R_f = 0.10. MS (electrospray): exact mass calculated for $\text{C}_{31}\text{H}_{28}\text{ClN}_5\text{O}_2$, 547.27; m/z found, 548.3. ^1H NMR (400MHz, CDCl_3): 7.64 (m, 1H), 7.43 (m, 2H), 7.16 (m, 2H), 6.72 (s, 1H), 6.50 (m, 1H), 4.88 (m, 1H), 4.73 (s, 1H), 4.28 (m, 2H), 4.13 (m, 2H), 3.92 (m, 2H), 3.47 (m, 3H), 3.09 (m, 6H), 2.55 (m, 6H), 2.27 (m, 3H), 1.84 (m, 4H).

EXAMPLE 6



5 (S)-1-(1-(3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl)-piperidin-4-yl)-6-chloro-1,3-dihydro-benzoimidazol-2-one.

10 A. (R)-1-[3-(4-Chloro-3-methyl-phenyl)-1-(2,3-dihydroxy-propyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

A solution of KHMDS (0.5 M, 8.4 mL, 4.1 mmol) was added to a solution of 1-[3-(4-chloro-3-methyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone (1.01 g, 3.49 mmol) in DMF (8.5 mL). The mixture was stirred for 1h then (2R)-1-tert-butyldimethylsilylglycidol (1.97 g, 10.5 mmol) was added. The mixture was stirred for 17 h then partitioned between EtOAc (500 mL) and saturated aqueous NaHCO₃ (100 mL). The EtOAc layer was washed with H₂O (3 x 100 mL), and brine (100 mL). The combined washes were extracted with EtOAc (2 x 100 mL). The combined extracts were dried over Na₂SO₄ and concentrated. The residue was dissolved in MeOH (50 mL) and treated with CSA (171 mg). The resulting mixture was stirred for 24 h then concentrated to near dryness. The residue was diluted with EtOAc (300 mL), washed with NaHCO₃ (100 mL), dried over Na₂SO₄ and concentrated. Flash chromatography (silica, 5-10% MeOH/CH₂Cl₂) provided 652 mg (50%) of the non-racemic diol. TLC (silica, 10% MeOH/CH₂Cl₂): R_f = 0.2. MS (electrospray): m/z calculated for C₁₈H₂₃³⁵ClN₃O₃ ([M+H]⁺, 364.14, found 364.1.

B. (R)-1-[3-(4-Chloro-3-methyl-phenyl)-1-oxiranylmethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

(*R*)-1-[3-(4-Chloro-3-methyl-phenyl)-1-(2,3-dihydroxy-propyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-*c*]pyridin-5-yl]-ethanone (452 mg, 1.24 mmol) and pyridinium *p*-toluenesulfonate (85 mg) were combined in MeC(OMe)₃ (50 mL) and briefly sonicated. The mixture was stirred for 17 h, concentrated, and the residue dissolved in CH₂Cl₂ (8 mL). The solution was cooled to 0 °C and treated with AcBr (0.15 mL, 2.0 mmol). After 5 h the mixture was partitioned between EtOAc (300 mL) and saturated aqueous NaHCO₃ (75 mL). The EtOAc layer was washed with H₂O (75 mL) and brine (75 mL), dried over Na₂SO₄ and concentrated. The residue was combined with K₂CO₃ (243 mg, 1.84 mmol) in MeOH (50 mL) and stirred for 3 h then worked up as described above. Purification by column chromatography (silica, 10-40% acetone/CH₂Cl₂) gave 159 mg (37%) of the title compound. Chiral HPLC (Daicel OD, 0.5% Et₂NH/MeOH) analysis indicated >95% optical purity. HPLC (reverse phase conditions), *t*_R = 4.97 min. MS (electrospray): exact mass calculated for C₁₈H₂₀ClN₃O₂ [M⁺+Na], 368.11; *m/z* found 368.05. ¹H NMR (CDCl₃, 400 MHz, a mixture of amide rotamers): 7.54 (br d, *J* = 6.3 Hz, 2H), 7.41-7.35 (m, 3H), 7.29 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.81 and 4.74 (A and B of AB quartet, *J*_{ab} = 15.7 Hz, 2H), 4.60 (s, 2H), 4.48 (dd, *J* = 15.2, 2.4 Hz, 1H), 4.42 (dd, *J* = 15.4, 2.8 Hz, 1H), 4.13 (t, *J* = 4.7 Hz, 1H), 4.09 (dd, *J* = 4.6 Hz, 1H), 3.93 (m, 2H), 3.74 (t, *J* = 5.8 Hz, 1H), 3.73 (t, *J* = 5.8 Hz, 1H), 3.34 (m, 2H), 2.85-2.75 (m, 6H), 2.53 (dd, *J* = 4.6, 2.5 Hz, 1H), 2.48 (dd, *J* = 4.6, 2.6 Hz, 1H), 2.43 (s, 3H), 2.41 (s, 3H), 2.20 (s, 3H), 2.15 (s, 3H).

C. 4-(5-Chloro-2-nitro-phenylamino)-piperidine-1-carboxylic acid ethyl ester.

To a solution of 2.03 g (11.6 mmol) of 4-chloro-2-fluoro-nitrobenzene in DMF (12.0 mL) at rt was added 2.00 g (11.6 mmol) of ethyl 4-amino-1-piperidinecarboxylate. A yellow precipitate formed within 30 min and the reaction was further diluted with DMF (12.0 mL) and CH₂Cl₂ (5.0 mL) and was shaken at 300 RPM overnight. The solvent was removed under reduced pressure and the resulting solid was dried under vacuum. The crude product was purified by flash chromatography (silica, 0-5% MeOH/CH₂Cl₂) to afford 2.83 g (81%) of the title compound. TLC (silica, 5% MeOH/CH₂Cl₂): *R*_f = 0.4. MS (electrospray): *m/z* calculated for C₁₄H₁₈ClN₃O₄ [M⁺+Na] 350.09, observed

350.0. ^1H NMR (400 MHz, CDCl_3): 8.13 (apparent d, $J = 9.1$ Hz, 2H), 6.84 (d, $J = 2.0$ Hz, 1H), 6.62 (dd, $J = 9.4, 2.3$ Hz, 1H), 4.15 (q, $J = 14.9, 7.3$ Hz, 2H), 4.08 (br d, $J = 12.4$ Hz, 2H), 3.70-3.58 (m, 1H), 3.17-3.05 (m, 2H), 2.07 (br dd, $J = 13.1, 3.1$ Hz, 2H), 1.63-1.50 (m, 2H), 1.28 (t, $J = 7.0$ Hz, 3H).

5

D. 4-(6-Chloro-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid ethyl ester.

To a stirred solution of 0.50 g (1.52 mmol) of 4-(5-chloro-2-nitro-phenylamino)-piperidine-1-carboxylic acid ethyl ester in EtOH (15.0 mL) was added
 10 concentrated HCl (3.0 mL) followed by 0.99 g (15.2 mmol) of zinc powder. After 1 h, additional concentrated HCl (1.5 mL) followed by 0.99 g (15.2 mmol) of zinc powder was added and the reaction was stirred for 1.5 h. The mixture was filtered through a pad of celite and was washed with 5% MeOH/ CH_2Cl_2 . The mixture was diluted with saturated NaHCO_3 and a precipitate formed. The
 15 layers were separated and the aqueous phase was extracted (3 x 5% MeOH/ CH_2Cl_2). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure to afford a brown oil. The crude oil was diluted with CH_2Cl_2 (15.0 mL) and 0.64 mL (4.56 mmol) of Et_3N was added followed by 0.45 g (1.52 mmol) of triphosgene. The reaction was
 20 allowed to stir overnight and was then diluted with 1 N NaOH (20 mL) and stirred for an additional 1 h. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (silica, 0-5% MeOH/ CH_2Cl_2) afforded 0.33
 25 g (67% over 2 steps) of the title compound. TLC (silica, 5% MeOH/ CH_2Cl_2): $R_f = 0.5$. MS (electrospray): m/z calculated for $\text{C}_{15}\text{H}_{18}\text{ClN}_3\text{O}_3$ [$\text{M}^+ + \text{Na}$] 346.10, observed 346.0. ^1H NMR (400 MHz, CDCl_3): 9.41 (s, 1H), 7.11 (d, $J = 2.0$ Hz, 1H), 7.04 (d, $J = 1.8$ Hz, 1H), 7.02 (s, 1H), 4.48-4.33 (m, 3H), 4.20 (q, $J = 7.1$ Hz, 2H), 2.92 (t, $J = 12.5$ Hz, 2H), 2.30 (dq, $J = 12.9, 4.6$ Hz, 2H), 2.10 (d, $J =$
 30 12.6 Hz, 2H), 1.31 (t, $J = 7.1$ Hz, 3H).

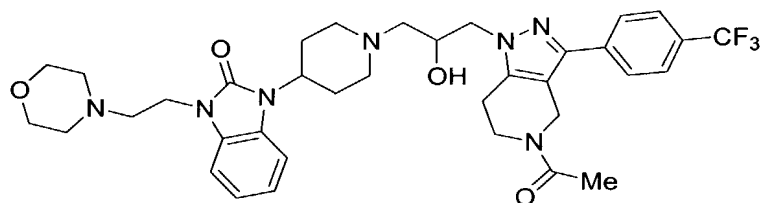
E. 6-Chloro-1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one.

A suspension of 0.20 g (0.62 mmol) of 4-(6-chloro-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid ethyl ester in 10% NaOH (0.62 mL) was heated to 105 °C for 6 h and then cooled. The solution was adjusted to pH 1 (conc. HCl) and then back to pH 10 (NaOH). Then, the mixture was diluted with 5% MeOH/CH₂Cl₂ (~30 mL) until both layers were clear. The layers were separated and the aqueous phase was extracted with 5% MeOH/CH₂Cl₂ (2 x 30 mL). The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure to afford 0.12 g (76%) of a light brown solid. TLC (silica, 10% MeOH/CH₂Cl₂): R_f = 0.1. MS (electrospray): *m/z* calculated for C₁₂H₁₄ClN₃O [M⁺+H] 252.08, observed 252.1. ¹H NMR (400 MHz, CDCl₃): 7.27 (d, *J* = 1.6 Hz, 2H), 7.02 (d, *J* = 1.6 Hz, 1H), 7.01 (s, 1H), 4.38 (m, 1H), 3.30 (br d, *J* = 11.9 Hz, 2H), 2.82 (dt, *J* = 12.3, 2.0 Hz, 2H), 2.35 (dq, *J* = 12.3, 3.5 Hz, 2H), 1.85 (br dd, *J* = 12.1, 2.1 Hz, 2H).

F. (S)-1-(1-(3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl)-piperidin-4-yl)-6-chloro-1,3-dihydro-benzoimidazol-2-one.

(*R*)-1-[3-(4-Chloro-3-methyl-phenyl)-1-oxiranylmethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone (31 mg, 0.10 mmol) and 6-chloro-1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (36 mg, 0.17 mmol) were combined in EtOH (0.3 mL) and heated to 70 °C. After 18 h the mixture was allowed to cool, diluted with CH₂Cl₂ and purified by preparative TLC (silica, 8% MeOH/CH₂Cl₂) to give 7 mg (12%) of the title compound. HPLC (reverse phase conditions), *t*_R = 3.49 min. MS (electrospray): *m/z* calculated for C₃₀H₃₅³⁵Cl₂N₆O₃ [M⁺+H] 597.22, found 597.20. ¹H NMR (CDCl₃, 400 MHz, a mixture of amide rotamers): 9.16 (br d, *J* = 10.1 Hz, 1H), 7.55 (br m, 1H), 7.40-7.28 (m, 2H), 7.18 (br s, 1H), 7.03 and 6.98 (A and B of ABX (with fine splittings), *J*_{ab} = 8.4 Hz, 2H), 4.85 and 4.74 (A and B of ABX (with fine splittings), *J*_{ab} = 15.7 Hz, 1H), 4.62 (s, 1H), 4.29-4.18 (m, 4H), 4.09-4.00 (m, 2H), 3.91-3.71 (m, 2H), 3.16-2.78 (m, 4H), 2.55-2.50 (m, 4H), 2.43 (s, 1.5H), 2.41 (s, 1.5H), 2.23 (m, 1H), 2.21 (s, 1.5H), 2.16 (s, 1.5H), 1.84 (br s, 2 H).

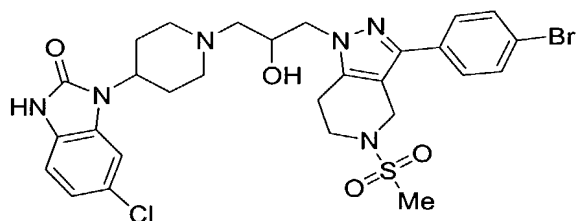
EXAMPLE 7



1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-(2-morpholin-4-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one.

A solution of 1-(1-{3-[5-acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one (130 mg, 0.22 mmol) in DMF (1 mL) was treated with cesium carbonate (146 mg, 0.45 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (329 mg, 2.2 mmol) at 25 °C and stirred for 24 h before it was diluted with EtOAc (10 mL) and H₂O (5 mL). The organic layer was separated, washed with H₂O (2 x 5 mL), dried over Na₂SO₄, and concentrated. Column chromatography (silica, 5% MeOH/CH₂Cl₂) afforded 124 mg (81%) of a white powder. TLC (10% MeOH/CH₂Cl₂): R_f = 0.31. MS (electrospray): *m/z* 696.3 ([M+H]⁺, C₃₆H₄₄F₃N₇O₄ requires 695.3). ¹H NMR (CDCl₃, 400 MHz, a mixture of two rotamers): 7.82 and 7.65 (AB pattern, *J*_{ab} = 8.2 Hz, 2H), 7.74 and 7.68 (AB pattern, *J*_{ab} = 8.4 Hz, 2H), 7.23-7.05 (m, 4H), 4.92 and 4.80 (AB pattern, *J*_{ab} = 15.6 Hz, 1.2H), 4.69 (s, 0.8H), 4.38-4.00 (m, 5H), 4.02 (t, *J* = 7.0 Hz, 2H), 3.92-3.70 (m, 2H), 3.70 (t, *J* = 4.5 Hz, 4H), 3.15-2.80 (m, 4H), 2.70 (t, *J* = 7.1 Hz, 2H), 2.60-2.20 (m, 9H), 2.24 (s, 1.6H), 2.18 (s, 1.4H), 1.85-1.75 (m, 2H).

EXAMPLE 8



1-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-1,3-dihydro-benzoimidazol-2-one.

5

A. 3-(4-Bromo-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester.

To a stirred solution of 500.0 g (2.51 mol) of 1-*tert*-butoxycarbonyl-4-piperidone and 87.1 g (2.76 mol) of morpholine in benzene (1.25 L) was added a catalytic amount (~ 0.25 g) of *p*-TsOH. The mixture was heated to reflux for 36 h with a Dean-Stark trap. The solvent was removed under reduced pressure to give a brown oil, which solidified on standing. The crude product was divided and 335.0 g (1.25 mol) of the enamine was diluted with CH₂Cl₂ (1.25 L) and 175.0 mL (1.25 mol) of Et₃N was added. The mixture was cooled to 0 °C and a solution of 275.0 g (1.25 mol) of 4-bromobenzoyl chloride in CH₂Cl₂ (150 mL) was added slowly by dropping funnel over 1 h. The mixture was allowed to warm to rt and stir overnight. The reaction was then diluted with 1 N HCl (450 mL) and stirred vigorously for 3 h. The aqueous layer was extracted with CH₂Cl₂ (3 x 500 mL) and the combined extracts were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude oil was diluted with EtOH (850 mL) and cooled to 0 °C. To this stirred solution was slowly added 120.0 g (3.75 mol) of hydrazine and the mixture was allowed to warm to rt and stir overnight during which time a white precipitate formed. The volume of the reaction was reduced to ~350 mL and EtOAc (1.50 L) was added to the mixture. The suspension was stirred vigorously for 2 h and was filtered then washed with EtOAc (2 x 500 mL) and dried under vacuum to afford 309.0 g (62% over 3 steps) of a white solid. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.3. MS (electrospray): *m/z* calculated for C₁₇H₂₀BrN₃O₂ [M⁺+H] 378.07, observed 378.0. ¹H NMR (400 MHz, CDCl₃): 7.65-7.26 (m, 4H), 4.64 (br s, 2H), 3.84-3.68 (br m, 2H), 2.87-2.74 (br m, 2H), 1.48 (br s, 9H).

B. 3-(4-Bromophenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridinium trifluoroacetate.

To a stirred solution of 10.0 g (26.4 mmol) of the 3-(4-bromo-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester in CH₂Cl₂ (26.0 mL) was added 26.0 mL of TFA. The resulting mixture was allowed to stir overnight. The solvent was removed under reduced pressure and the solid was dried in vacuo. The dried solid was suspended in Et₂O and stirred vigorously for 2 h and then filtered and dried in vacuo to give 10.1 g of a white solid, which was used without further purification. TLC (silica, 10% MeOH/CH₂Cl₂): R_f = 0.05. MS (electrospray): *m/z* calculated for C₁₂H₁₂BrN₃ [M⁺+H] 278.02, observed 278.0.

C. 3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine.

To a stirred solution of 3.11 g (11.1 mmol) of 3-(4-bromophenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridinium trifluoroacetate and 4.71 mL (33.5 mmol) of Et₃N in DMF (55 mL) was slowly added 1.21 mL (15.6 mmol) of methanesulfonyl chloride. After 2.5 h, the solvent was removed under reduced pressure and the residue was diluted with CH₂Cl₂ (100 mL) and saturated NaHCO₃ (100 mL). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 30 mL). The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. Purification by column chromatography (silica, 0-5% MeOH/CH₂Cl₂) afforded 2.01 g (50%) of the title compound. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.3. MS (electrospray): *m/z* calculated for C₁₃H₁₄BrN₃O₂S [M⁺+H] 356.00, observed 356.0.

D. 3-(4-Bromo-phenyl)-5-methanesulfonyl-1-oxiranylmethyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine.

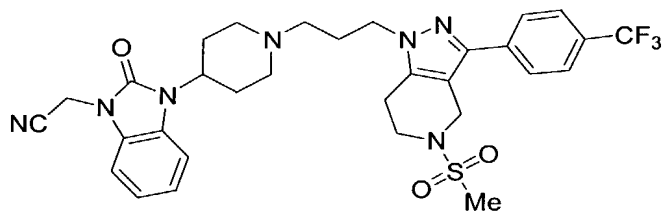
To a stirred solution of 2.50 g (7.00 mmol) of 3-(4-bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine and 5.52 mL (70.0 mmol) of epichlorohydrin was added 2.50 g (7.72 mmol) of solid Cs₂CO₃. The reaction was allowed to stir for 48 h and the solvent was removed under reduced pressure. The residue was then diluted with H₂O (150 mL) and EtOAc (150 mL). The layers were separated, and the organic layer was washed with

H₂O (50 mL) and brine (50 mL), dried over Na₂SO₄ and the solvent was removed under reduce pressure. Purification by flash chromatography (silica, 0-20% acetone/CH₂Cl₂) afforded 1.52 g (53%) of a white solid. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.5. MS (electrospray): *m/z* calculated for C₁₆H₁₈BrN₃O₃S [M⁺+H] 412.03, observed 412.0. ¹H NMR (400 MHz, CDCl₃): 7.54 and 7.47 (A and B of AA'BB', *J* = 8.6 Hz, 4H), 4.56-4.45 (m, 3H), 4.10 (dd, *J* = 15.1, 5.4 Hz, 1H), 3.73-3.58 (m, 2H), 3.38-3.32 (m, 1H), 2.96-2.87 (m, 2H), 2.86 (s, 3H), 2.83 (dd, *J* = 4.4, 4.2 Hz, 1H), 2.48 (dd, *J* = 4.6, 2.6 Hz, 1H).

10 E. 1-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-1,3-dihydro-benzoimidazol-2-one.

A stirred solution of 25.0 mg (0.061 mmol) of 3-(4-bromo-phenyl)-5-methanesulfonyl-1-oxiranylmethyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine and 19.0 mg (0.073 mmol) of 6-chloro-1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one in EtOH (0.5 mL) was heated to 80 °C in a sealed vessel for 16 h. The reaction was cooled and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica, 0-5% MeOH/CH₂Cl₂) to afford 0.025 g (63%) of the title compound. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.4. MS (electrospray): *m/z* calculated for C₂₈H₃₂BrClN₆O₄S [M⁺+H] 663.11, observed 663.0. ¹H NMR (400 MHz, CDCl₃): 10.2 (s, 1H), 7.52 and 7.46 (A and B of AA'BB', *J* = 8.6 Hz, 4H), 7.15 (br d, *J* = 1.5 Hz, 1H), 7.04-6.95 (m, 2H), 4.52 and 4.49 (A and B of AB quartet, *J*_{ab} = 14.5 Hz, 2H), 4.33-4.14 (m, 3H), 4.07-3.97 (m, 1H), 3.74-3.58 (m, 2H), 3.17-2.89 (m, 4H), 2.86 (s, 3H), 2.57-2.30 (m, 5H), 2.20 (t, *J* = 11.1 Hz, 1H), 1.87-1.73 (m, 2H).

EXAMPLE 9



5 [3-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-acetonitrile.

10 A. 3-(4-Trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester.

To a stirred solution of 500 g (2.51 mol) of 1-*tert*-butoxycarbonyl-4-piperidone and 87.1 g (2.76 mol) of morpholine in benzene (1.25 L) was added a catalytic amount (~ 0.25 g) of *p*-TsOH. The mixture was heated to reflux for 36 h with a Dean-Stark trap. One half of the solvent was removed under reduced pressure and the resulting solution was cooled and filtered. The filtrate was then concentrated to yield 630 g (94%) of an orange red oil. The enamine was divided and 320 g (1.19 mol) was diluted with CH₂Cl₂ (1.0 L) and 165.0 mL (1.19 mol) of Et₃N was added. The mixture was cooled to 0 °C and a solution of 225 g (1.08 mol) of 4-trifluoromethylbenzoyl chloride in CH₂Cl₂ (0.5 L) was added slowly by dropping funnel over 1h. The mixture was allowed to warm to rt and stir overnight. The reaction was then diluted with 1 N HCl (450 mL) and stirred vigorously for 3 h. The aqueous layer was extracted with CH₂Cl₂ (3 x 500 mL) and the combined extracts were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude oil was diluted with EtOH (1 L) and cooled to 0 °C. To this stirred solution was slowly added 115 g (3.57 mol) of hydrazine and the mixture was allowed to warm to rt and stir overnight during which time a white precipitate formed. The volume of the reaction was reduced to ~500 mL and cooled. The precipitate was collected to afford 285 g (72% from enamine) of a white solid. ¹H NMR (400 MHz, CDCl₃): 7.63-7.55

(m, 4H), 4.58 (br s, 2H), 3.69-3.62 (br m, 2H), 2.74-2.68 (br m, 2H), 1.47 (s, 9H).

B. 1-(2-Methoxycarbonyl-ethyl)-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester.

3-(4-Trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (1.85g, 5.04 mmol) and methyl acrylate (0.50 mL, 5.6 mmol) were combined in toluene (30 mL) and heated to 75 °C. The resulting mixture was treated with *t*-BuONa (100 mg), and heating continued for 48 h. The mixture was allowed to cool and partitioned between EtOAc (300 mL) and NaHCO₃ (75 mL). The aqueous layer was extracted with EtOAc (3 x 75 mL). The combined extracts were dried over Na₂SO₄ and concentrated. Column chromatography (silica, 30-60% EtOAc/hexanes) afforded 343 mg (15%) of the title compound. TLC (silica, 50% EtOAc/hexanes): *R_f* = 0.4. MS (electrospray): *m/z* calculated for C₂₂H₂₇F₃N₃O₄ [*M*⁺+H] 454.20, found 454.1. ¹H NMR (CDCl₃, 400 MHz): 7.75 (br d, *J* = 8.1 Hz, 2H), 7.64 (br s, 2H), 4.63 (br s, 2H), 4.30 (t, *J* = 6.6 Hz, 2H), 3.75 (br s, 2H), 3.68 (s, 3H), 2.98 (t, *J* = 6.6 Hz, 2H), 2.79 (br t, *J* = 5.6 Hz, 2H), 1.48 (s, 9H).

C. 1-(3-Hydroxy-propyl)-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester.

A solution of LiBH₄ (26 mg, 1.2 mmol) in THF (0.5 mL) was added to a 0 °C solution of 1-(2-methoxycarbonyl-ethyl)-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (317 mg, 0.70 mmol) in THF (4.0 mL). The mixture was stirred for 5 min then additional LiBH₄ (15 mg) was added and stirring continued for 17 h. The mixture was partitioned between EtOAc (80 mL) and saturated aqueous NaHCO₃ (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined extracts were dried over Na₂SO₄ and concentrated. Column chromatography (silica, 0-8% MeOH/CH₂Cl₂) afforded 268 mg (95%) of the title compound. HPLC (reverse phase conditions), *t_R* = 6.82 min. MS (electrospray): *m/z* calculated for C₂₁H₂₆F₃N₃O₃ [*M*⁺+Na] 448.18, found 448.10. ¹H NMR (CDCl₃, 400 MHz): 7.73 (br d, *J* = 8.2 Hz, 2H), 7.65 (br s, 2H), 4.64 (br s, 2H), 4.21 (t, *J*

= 6.4 Hz, 2H), 3.76 (br s, 2H), 3.66 (t, J = 5.7 Hz, 2H), 2.73 (br t, J = 5.4 Hz, 2H), 2.04 (q, J = 6.1, 2H), 1.48 (s, 9H).

D. 4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester.

1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (7.24 g, 34.1 mmol) and di-tert-butyl dicarbonate (9.12 g, 41.0 mmol) were combined in DMF (80 mL) and the mixture heated to 40 °C under N₂ for 17 h. The mixture was allowed to cool, diluted with EtOAc (800 mL) and washed with saturated aq. NaHCO₃ (150 mL), H₂O (3 x 150 mL) and brine (150 mL). The combined aqueous washes were extracted with EtOAc (2 x 150 mL). The combined extracts were dried over Na₂SO₄ and concentrated to afford 12.4 g of the title compound. TLC (silica, 50% EtOAc/hexanes): R_f = 0.3. MS (electrospray): m/z calculated for C₁₇H₂₃N₃O₃ [M⁺+Na] 340.16, found 340.1. ¹H NMR (CDCl₃, 400 MHz): 10.59 (s, 1H), 7.15-7.11 (m, 2H), 7.08-7.02 (m, 2H), 4.49 (tt, J = 8.4, 4.0 Hz, 1H), 4.32 (br s, 2H), 2.89 (br t, J = 11.6, 2H), 2.34 (dq, J = 12.6, 4.4 Hz, 2H), 1.83 (br d, J = 10.5 Hz, 2H) 1.36 (s, 9H).

E. (2-Oxo-3-piperidin-4-yl-2,3-dihydro-benzoimidazol-1-yl)-acetonitrile.

A solution of 4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (2.91 g, 9.16 mmol) in THF (10 mL) was added dropwise to a solution of KHMDS (2.19 g, 11.0 mmol) in THF (20 mL). The mixture was stirred for 10 min then bromoacetonitrile (3.2 mL, 46 mmol) was added. The resulting mixture was stirred for 4 h then partitioned between EtOAc (750 mL) and saturated aqueous NaHCO₃ (200 mL). The EtOAc layer was washed with H₂O (3 x 200 mL) and brine (200 mL). The combined washes were extracted with EtOAc (2 x 150 mL). The combined extracts were dried over Na₂SO₄ and concentrated. Column chromatography (silica, 20-60% EtOAc/hexanes) afforded 2.20 g (67%) of 4-(3-cyanomethyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester. The purified material was dissolved in CH₂Cl₂ (40 mL) and diluted with TFA (25 mL). The resulting mixture was stirred for 1 h then diluted with CH₂Cl₂ (250 mL) and washed with 1 N NaOH (100 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 100

mL). The combined extracts were dried over Na₂SO₄ and concentrated to 1.59 g (95%) of the title compound which was suitable for further use without purification. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.1. MS (electrospray): *m/z* calculated for C₁₄H₁₇N₄O [M⁺+H] 257.14, found 257.1. ¹H NMR (CDCl₃, 400 Hz): 7.33-7.29 (m, 1H), 7.17-7.02 (m, 3H), 4.75 (s, 2H), 4.41 (tt, *J* = 12.2, 4.4 Hz, 1H), 3.28 (br d, *J* = 9.8 Hz, 2H), 3.11 (br s, 1H), 2.80 (t, *J* = 10.0 Hz, 2H), 2.37 (dq, *J* = 12.5, 4.2 Hz, 2H), 1.83 (br d, *J* = 11.8 Hz, 2H).

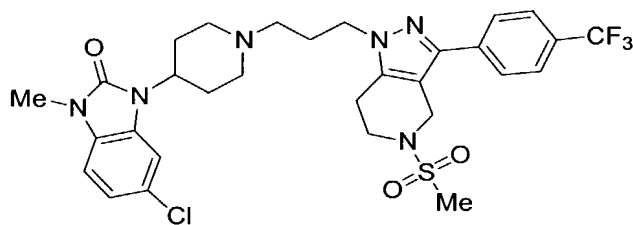
F. [3-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-acetonitrile.

1-(3-Hydroxy-propyl)-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (268 mg, 0.63 mmol) was dissolved in CH₂Cl₂ (10 mL) and TFA (10 mL). The mixture was stirred for 1 h then concentrated to dryness. The residue was dissolved in CH₂Cl₂ (4.0 mL), cooled to 0 °C and treated with *i*-Pr₂NEt (0.36 mL, 2.1 mmol), followed by methanesulfonyl chloride (0.16 mL, 2.1 mmol). The reaction mixture was stirred for 4 h, then diluted with EtOAc (200 mL) and washed with saturated aqueous NaHCO₃ (2 x 25 mL). The washes were extracted with EtOAc (2 x 25 mL). The combined extracts were dried over Na₂SO₄ and concentrated. A portion of the crude mesylate (197 mg, ca. 0.41 mmol) was combined with (2-oxo-3-piperidin-4-yl-2,3-dihydro-benzoimidazol-1-yl)-acetonitrile (321 mg, 1.25 mmol) in CH₂Cl₂ (2.0 mL) and DMF (0.5 mL). The resulting mixture was treated with *i*-Pr₂NEt (0.22 mL, 1.3 mmol) and stirred for 60 h. The reaction mixture was partitioned between EtOAc (150 mL) and saturated aqueous NaHCO₃ (75 mL). The EtOAc layer was washed with H₂O (2 x 75 mL), and brine (75 mL). The combined washes were extracted with EtOAc (3 x 50 mL). The combined extracts were dried over Na₂SO₄ and concentrated. Purification of the residue by preparative TLC (silica, 1% MeOH/CH₂Cl₂ then 25% acetone/CH₂Cl₂) gave 37 mg (14%) of the title compound. HPLC (reverse phase conditions), *t*_R = 2.94 min. MS (electrospray): *m/z* calculated for C₃₁H₃₅F₃N₇O₃S [M⁺+H] 642.25, found 642.25. ¹H NMR (CDCl₃, 400 MHz): 7.73 and 7.76 (A and B of AA'BB' *J*_{ab} = 8.2 Hz, 4H), 7.26-7.05 (m, 4H), 4.81 (s, 2H), 4.56 (s, 2H), 4.26 (m, 1H),

4.15 (t, J = 6.8 Hz, 2H), 3.70 (t, J = 5.8 Hz, 2H), 3.03 (br d, J = 11.1 Hz, 2H), 2.95 (t, J = 5.7 Hz, 2H), 2.91 (s, 3H), 2.43 (m, 4H), 2.12 (m, 4H), 1.82 (br d, J = 9.9 Hz, 2H).

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EXAMPLE 10



10 5-Chloro-3-(1-{3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-benzoimidazol-2-one.

A. 1-Methanesulfonyl-piperidin-4-one.

15 Potassium carbonate (324 g, 2340 mmol) was added to a solution of 4-piperidone monohydrate hydrochloride (90 g, 586 mmol) in chloroform (300 mL) and water (300 mL). The slurry was cooled to 0 °C and treated with methylsulfonyl chloride (136 mL, 1760 mmol) by dropwise addition over a 1 h period. The reaction mixture was allowed to shake for 72 h and was

20 partitioned between CH₂Cl₂ (500 mL) and saturated aqueous NaHCO₃ (500 mL). The aqueous layer was extracted with CH₂Cl₂ (3 X 200 mL). The organic layer was washed with 1% KHSO₄ (250 mL), dried (Na₂SO₄), and concentrated to afford 90.5 g (87%) of a white solid. HPLC (reverse phase conditions), t_R = 2.19 min. MS (electrospray): exact mass calculated for C₆H₁₁NO₃S, 177.1; m/z found, 178.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): 3.60 (t, J = 6.5 Hz, 4H), 2.89 (s, 3H), 2.59 (t, J = 6.3 Hz, 4H).

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B. 5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine.

p-Toluenesulfonic acid (1.34 g, 7.0 mmol) and morpholine (25.83 mL, 296 mmol) were added to a solution of 1-methanesulfonyl-piperidin-4-one (50.0 g, 282 mmol) in benzene (282 mL). The reaction mixture was heated in a flask equipped with a condenser and a Dean-Stark trap at reflux for 15 h. The reaction mixture was cooled and concentrated in vacuo to give the enamine which was used without further purification. The enamine was dissolved in CH₂Cl₂ (200 mL) and cooled to 0 °C. To this was added triethylamine (47.2 mL, 339 mmol) followed by dropwise addition of 4-trifluoromethylbenzoyl chloride (42.3 mL, 285 mmol) dissolved in CH₂Cl₂ (82 mL). The reaction mixture was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was washed with 1 N HCl (250 mL) and the CH₂Cl₂ layer was separated, dried (Na₂SO₄), and concentrated. The resulting oil was taken up in ethanol (300 mL) and treated with hydrazine (44.3 mL, 1.41 mol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was concentrated and the resulting solid was filtered with ethanol wash and dried in vacuo to afford 70 g (72%) of 5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine as a white solid. HPLC (reverse phase conditions), *t*_R = 6.33 min. MS (electrospray): exact mass calculated for C₁₄H₁₄F₃N₃O₂S, 345.0; *m/z* found, 346.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): 7.72 (s, 4H), 4.58 (s, 2H), 3.69 (t, *J* = 5.7 Hz, 2H), 2.99 (t, *J* = 5.7 Hz, 2H), 2.92 (s, 3H).

C. 3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propan-1-ol.

Cs₂CO₃ (33.74 g, 103.5 mmol) was added to a solution of 5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (29.8 g, 86.3 mmol) in anhydrous DMF (70 mL) and stirred for 25 min. 3-Bromo-1-propanol (8.6 mL, 13.2 g, 94.9 mmol) was added and stirred under N₂ at room temperature for 18 h. Water (500 mL) was added to the reaction and stirred for 5 min. The precipitated material was filtered out and washed with water (4 X 100 mL) and dried in a Freeze Drying System. The crude material (31.0 g) was

taken up in anhydrous DMF (65 mL) and Cs_2CO_3 (33.74 g, 103.5 mmol) was added, and stirred for 10 min. 3-Bromo-1-propanol (8.6 mL, 13.2 g, 94.9 mmol) and MeOH (6.0 mL, 4.75 g, 148 mmol) were added and stirring continued under N_2 at rt for 15 h. Water (500 mL) was added to the reaction and stirred for 10 min. The precipitated material was filtered and washed with water (3 X 100 mL). The filter cake was dissolved in CH_2Cl_2 (200 mL) and washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The solid was triturated with Et_2O (200 mL), filtered, then washed with Et_2O , and dried to furnish 16.0 g of the desired compound. The mother liquor was chromatographed (silica, 0-10% acetone/ EtOAc) to obtain an additional 3.0 g of the title compound. The combined yield was 54.6%. MS (electrospray): exact mass calculated for $\text{C}_{17}\text{H}_{20}\text{F}_3\text{N}_3\text{O}_3\text{S}$, 403.12; m/z found, 404.0 $[\text{M}+\text{H}]^+$, 426.0 $[\text{M}+\text{Na}]^+$. ^1H NMR (400 MHz, CDCl_3): 7.71 (d, $J = 8.2$ Hz, 2H), 7.66 (d, $J = 8.5$ Hz, 2H), 4.55 (s, 2H), 4.23 (t, $J = 6.5$ Hz, 2H), 3.70-3.63 (m, 4H), 2.90 (s, 3H), 2.90 (t, $J = 5.1$ Hz, 2H), 2.62 (t, $J = 5.9$ Hz, 1H), 2.06 (q, $J = 6.1$ Hz, 2H).

D. 5-Chloro-1-methyl-3-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one.

To a stirred suspension of 0.97 g (2.99 mmol) of 4-(6-chloro-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid ethyl ester in THF (30 mL) was added 0.5 M KHMDS in toluene. This mixture was stirred for 1 h and 0.25 mL (3.89 mmol) of MeI was added in one portion. After 1.5 h the reaction was diluted with 1 N HCl (75 mL) and EtOAc (75 mL). The layers were separated, and the organic layer was washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure.

Purification by flash chromatography (silica, 0-5% MeOH/ CH_2Cl_2) afforded 0.92 g (91%) of a white solid. A suspension of 0.92 g (2.72 mmol) of the ethyl carbamate in 1:1 EtOH (7.0 mL) and 10% NaOH (7.0 mL) was heated to 110 °C for 36 h and then cooled. The mixture was diluted with EtOAc (30 mL) and H_2O . The layers were separated and the aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure to afford 0.56 g (78%) of a pale yellow solid. TLC (silica, 10% MeOH/ CH_2Cl_2): $R_f = 0.1$. MS (electrospray): m/z calculated for $\text{C}_{13}\text{H}_{16}\text{ClN}_3\text{O}$ $[\text{M}^++\text{H}]$ 266.10, observed 266.0.

¹H NMR (400 MHz, CDCl₃): 7.28 (d, *J* = 1.8 Hz, 2H), 7.05 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 4.41 (tt, *J* = 12.5, 4.3 Hz, 1H), 3.39 (s, 3H), 3.30 (br d, *J* = 11.9 Hz, 2H), 2.82 (dt, *J* = 12.4, 2.0 Hz, 2H), 2.30 (dq, *J* = 12.3, 4.3 Hz, 2H), 1.81 (br dd, *J* = 12.1, 2.3 Hz, 2H).

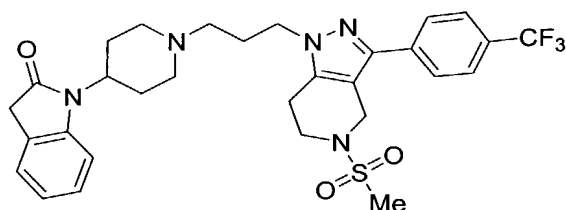
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E. 5-Chloro-3-(1-{3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-benzoimidazol-2-one.

To a stirred solution of 0.33 mL (3.72 mmol) of oxalyl chloride in CH₂Cl₂ (10 mL) under N₂ at -78 °C was added 0.36 mL (4.96 mmol) of DMSO and the reaction was stirred for 15 min. To this solution was added a solution of 1.0 g (2.48 mmol) of 3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propan-1-ol in 10 mL over 10 min and stirring was continued for 25 min. To this solution was added 1.40 mL (9.92 mmol) of Et₃N and the reaction was stirred for 10 min at -78 °C and was then allowed to warm to rt and stir for 1 h. The mixture was diluted with EtOAc (75 mL) and saturated NaHCO₃ (75 mL) and the layers were separated. The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The resulting solid was dried in vacuo and was suspended in Et₂O (20 mL) and stirred vigorously for 1 h. The solid was filtered and washed with Et₂O (2 x 10 mL) to afford the crude aldehyde which was carried on without further purification. The crude aldehyde, 5-chloro-1-methyl-3-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (0.60 g, 2.3 mmol), and 0.20 mL (3.72 mmol) of AcOH was dissolved in CH₂Cl₂ (15 mL) followed by 0.69 g (3.25 mmol) of NaBH(OAc)₃, and the reaction was allowed to stir overnight. The mixture was diluted with CH₂Cl₂ (75 mL) and saturated NaHCO₃ (75 mL) and the layers were separated. The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. Purification by flash chromatography (silica, 0-4% MeOH/CH₂Cl₂) afforded 1.28 g (79% over 2 steps) of a white solid. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.5. MS (electrospray): *m/z* calculated for C₃₀H₃₄ClF₃N₆O₃S [M⁺+H] 651.21, observed 651.2. ¹H NMR (400 MHz, CDCl₃): 7.71 and 7.63 (A and B of AA'BB", *J*_{AB} = 8.17 Hz, 4H), 7.16 (d, *J* = 1.8 Hz, 1H), 7.04 (d, *J* = 8.3, 1.8 Hz,

1H), 6.86 (d, $J = 8.3$ Hz, 1H), 4.55 (s, 2H), 4.23 (tt, $J = 12.4, 4.3$ Hz, 1H), 4.13 (t, $J = 6.7$ Hz, 2H), 3.69 (t, $J = 5.7$ Hz, 2H), 3.36 (s, 3H), 3.0 (d, $J = 11.6$ Hz, 2H), 2.95 (t, $J = 5.7$ Hz, 2H), 2.90 (s, 3H), 2.45-2.32 (m, 4H), 2.16-2.04 (m, 4H), 1.76 (dd, $J = 11.9, 2.0$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): 171.0, 153.7, 144.7, 137.1, 136.8, 129.3, 129.0, 128.7, 126.4, 125.5 (q, $J = 3.8$ Hz), 122.7, 120.7, 109.8, 109.2, 108.0, 60.3, 54.7, 53.0, 51.3, 46.8, 43.1, 42.4, 36.8, 29.0, 27.2, 27.0, 22.3, 21.0, 14.1.

EXAMPLE 11



1-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one.

A. Methyl 2-nitrophenylacetate.

2-Nitrophenylacetic acid (60 g, 0.3 mol) was set stirring in 250 mL of methanol. Sulfuric acid (0.5 mL) was added and the mixture heated to reflux. After 20 h the mixture was cooled and evaporated under reduced pressure to give a clear yellow oil. The oil was brought up in EtOAc and washed with saturated NaHCO_3 . The organics were dried (MgSO_4) and evaporated to give 63 g (98%) of the ester as a clear orange liquid. TLC (silica, 25% EtOAc/hexanes): $R_f = 0.36$. ^1H NMR (400MHz, CDCl_3): 8.24 (m, 1H), 7.16 (m, 1H), 7.60 (m, 1H), 7.47 (m, 1H), 4.15 (s, 2H), 3.83 (s, 3H).

B. Methyl 2-aminophenylacetate.

Methyl 2-nitrophenylacetate (10.1 g, 51.2 mmol) in 125 mL of methanol containing 221 mg of 10% Pd/C was placed on the Parr hydrogenator at 40 psi. After 5 h the mixture was filtered through celite and evaporated under

reduced pressure to give a clear red oil. The solvent was evaporated under reduced pressure to give 8.5 g (100%) of methyl 2-aminophenylacetate as a clear red oil. TLC (silica, EtOAc/hexanes): R_f = 0.24. ^1H NMR (400MHz, CDCl_3): 7.21 (m, 2H), 6.86 (m, 2H), 3.81 (s, 3H), 3.70 (s, 2H).

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C. 4-(2-Oxo-2,3-dihydro-indol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester.

Methyl 2-aminophenylacetate (3.0 g, 18.2 mmol) and 1-*tert*-butoxycarbonyl-4-piperidone (4.5 g, 22.6 mmol) were set stirring in 50 mL of CH_2Cl_2 under an atmosphere of nitrogen. Sodium triacetoxymethylborohydride (5.4 g, 25.5 mmol) was added followed by 1 mL of acetic acid. After 20 h at rt the mixture was quenched by the slow addition of saturated NaHCO_3 . After stirring for 30 min, the organics were separated, dried (MgSO_4), and evaporated to afford 7.5 g of a purple oil. Purification by column chromatography (silica, 10-50% EtOAc/hexanes) gave 3.9 g (62%) of the title compound. TLC (silica, 25% EtOAc/hexanes): R_f = 0.15. ^1H NMR (400MHz, CDCl_3): 7.25 (m, 2H), 7.01 (m, 2H), 4.40 (m, 1H), 3.53 (s, 2H), 2.83 (m, 2H), 2.32 (m, 2H), 1.70 (m, 2H), 1.51 (s, 9H).

15

D. 1-Piperidin-4-yl-1,3-dihydro-indol-2-one.

4-(2-Oxo-2,3-dihydro-indol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (3.9 g, 12.3 mmol) was set stirring in 30 mL of 1:1 TFA/ CH_2Cl_2 . After 45 min the solvent was evaporated under reduced pressure to give a clear purple oil. The oil was brought up in diethyl ether and cooled on ice to give a precipitate. The solid was filtered, washed with ether and air dried to give 4.0 g (100%) of the title compound as a TFA salt. ^1H NMR (400MHz, $\text{DMSO}-d_6$): 8.6 (br s, 1H), 7.27 (m, 3H), 7.03 (m, 1H), 4.45 (m, 1H), 3.56 (s, 2H), 3.42 (m, 2H), 3.09 (m, 2H), 2.53 (m, 2H), 1.78 (m, 2H).

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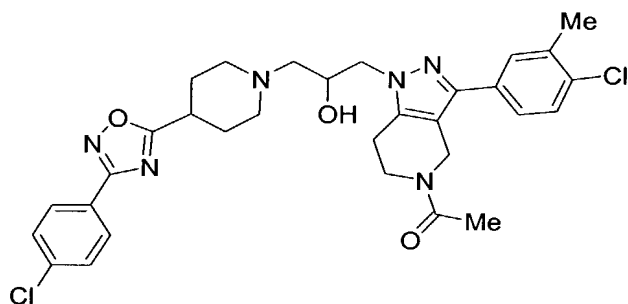
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E. 1-(1-(3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-1-yl]-propyl)-piperidin-4-yl)-1,3-dihydro-indol-2-one.

3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-1-yl]-propan-1-ol (304 mg, 0.754 mmol) was set stirring in 5 mL of CH_2Cl_2 at rt under nitrogen. Dess-Martin reagent (394 mg, 0.929

mmol) was added in one portion and the reaction mixture was left stirring. After 1.5 h the mixture was added to a stirring solution of thiosulphate (10 equiv) in 20 mL of water and 5 mL of saturated NaHCO_3 . After 2 h the organic layer was separated, dried (MgSO_4) and evaporated to give the aldehyde as a light yellow solid. The above aldehyde (303 mg, 0.754 mmol) and 1-piperidin-4-yl-1,3-dihydro-indol-2-one were set stirring in 15 mL of CH_2Cl_2 containing Et_3N (0.15 mL, 1.1 mmol). A solution of $\text{Na}(\text{AcO})_3\text{BH}$ in 5 mL of CH_2Cl_2 was added dropwise via pipette over 10 min and the mixture was left to stir overnight. The mixture was quenched with saturated NaHCO_3 and the organic layer separated. The organics were dried (MgSO_4) and evaporated to a clear purple oil. Purification with column chromatography (silica, 50-100% acetone/ CH_2Cl_2) gave 240 mg (53%) of a light pink solid. TLC (silica, 50% acetone/ CH_2Cl_2): $R_f = 0.17$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 7.82 (m, 4H), 7.24 (m, 2H), 7.11 (m, 1H), 6.98 (m, 1H), 4.49 (s, 2H), 4.12 (m, 3H), 3.54 (s, 2H), 3.32 (s, 4H), 2.95 (m, 7H), 2.32 (m, 4H), 1.99 (m, 4H), 1.55 (m, 2H).

EXAMPLE 12

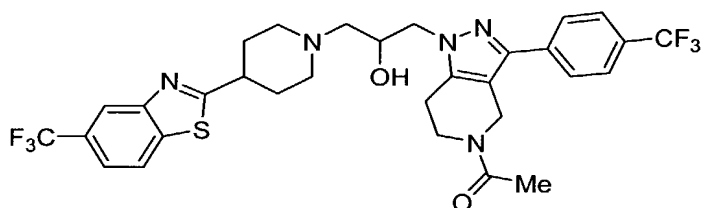


1-[3-(4-Chloro-3-methyl-phenyl)-1-(3-{4-[3-(4-chloro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-2-hydroxy-propyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

1-[3-(4-Chloro-3-methyl-phenyl)-1-oxiranylmethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone (0.069 g, 0.20 mmol) was dissolved in CH_2Cl_2 (1 mL), and 4-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]piperidine (0.105 g, 0.4 mmol) was added, followed by $\text{Yb}(\text{OTf})_3$ (0.031 g, 0.22 mmol). The mixture was stirred at room temperature for 16 h. Preparative TLC (silica,

7.5% MeOH/CH₂Cl₂) afforded 84 mg (69%) of the title compound. MS (electrospray): exact mass calculated for C₃₁H₃₄Cl₂N₆O₃, 608.21; *m/z* found, 609.2 [M⁺+H]. ¹H NMR (400 MHz, CDCl₃, 1:1 mixture of rotamers): 8.00 (d, *J* = 8.4 Hz, 2H), 7.56-7.53 (m, 1H), 7.48-7.42 (d, *J* = 8.6 Hz, 2H), 7.41-7.30 (m, 2H), 4.84 and 4.73 (A and B of AB quartet *J* = 15.6 Hz, 1H), 4.62 (br s, 1H), 4.25-4.13 (m, 2H), 4.10-3.98 (m, 2H), 3.90-3.70 (m, 2H), 3.04-2.71 (m, 5H), 2.51-2.40 (m, 6H), 2.30-2.15 (m, 6H), 2.10-1.90 (m, 2H).

EXAMPLE 13



1-[1-{2-Hydroxy-3-[4-(5-trifluoromethyl-benzothiazol-2-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

A. 2-Piperidin-4-yl-5-trifluoromethyl-benzothiazole.

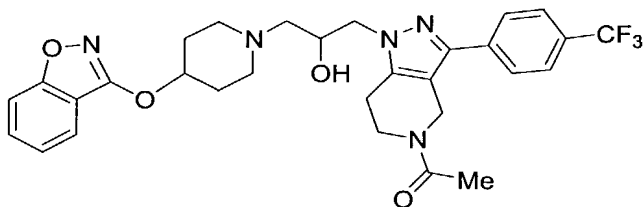
To a stirred solution of 5 g (29.2 mmol) of 1-acetyl-piperidine-4-carboxylic acid in toluene (100 mL) and a catalytic amount of DMF (1 mL) was added dropwise 2.4 mL of oxalyl chloride (33.3 mmol). The reaction mixture was allowed to stir at room temperature overnight. A 20 mL aliquot (6 mmol) of the acid chloride solution was then placed in a separate flask and treated with a solution of 1.4 g (6.10 mmol) of 2-amino-4-(trifluoromethyl)thiophene hydrochloride in triethyl amine (4 mL). The reaction was then heated to 80 °C for 30 min and then partitioned between ethyl acetate (50 mL) and water (20 mL) and separated. The aqueous layer was further extracted with EtOAc (2 x 30 mL). The combined organic layers were then washed with water (25 mL), brine, dried over Na₂SO₄, and the solvent was removed under reduced pressure. This was then heated to 60 °C in a 1 N HCl/MeOH solution overnight with stirring. The

reaction mixture was cooled and concentrated to dryness. The solid was then taken back up in 35 mL MeOH and stirred over sodium bicarbonate (1 g) for 1 h then filtered and stripped to give 1.05 g (60%) of the desired product which was used without further purification. MS (electrospray): exact mass calculated for $C_{13}H_{13}F_3N_2S$, 286.08; m/z found, 287.1 $[M+H]^+$. 1H NMR ($CDCl_3$, 400 MHz): 8.25 (s, 1H), 7.98 (d, $J = 8.41$ Hz, 1H), 7.65 (d, $J = 8.41$ Hz, 1H), 3.38 (tt, $J = 11.35, 4.11$ Hz, 1H), 3.28 (ddd, $J = 13.69, 11.74, 2.74$ Hz, 1H), 3.16 (ddd, $J = 13.89, 11.15, 2.74$ Hz, 1H), 2.85 (m, 1H), 2.25 (br m, 2H), 1.97 (br m, 2H).

- 10 B. 1-[1-{2-Hydroxy-3-[4-(5-trifluoromethyl-benzothiazol-2-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

A solution of 63 mg (0.22 mmol) 2-piperidin-4-yl-5-trifluoromethyl-benzothiazole was dissolved in 4 mL EtOH and treated with 40 mg (0.11 mmol) of 1-[1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone. The solution was heated to 60 °C overnight. The solvent was then removed by rotary evaporation and the crude product was purified by column chromatography (silica, 0-10% MeOH/EtOAc) to afford 57 mg (80%) of a white solid. MS (electrospray): exact mass calculated for $C_{31}H_{31}F_6N_5O_2S$, 651.21; m/z found, 652.2 $[M+H]^+$. 1H NMR ($CDCl_3$, 400 MHz, a mixture of amide rotamers): 8.24 (s, 1H), 7.97 (d, $J = 8.41$ Hz, 1H), 7.78 (d, $J = 8.41$ Hz, 1H), 7.70 (m, 2H), 7.65 (d, $J = 8.41$ Hz, 1H), 7.60 (dd, $J = 8.41, 1.37$ Hz, 1H), 4.88 and 4.76 (A and B of AB quartet, $J = 15.85$ Hz, 1H), 4.66 (br s, 1H), 4.25-4.15 (m, 2H), 4.08-3.99 (m, 1.5H), 3.91-3.83 (m, 0.5H), 3.82-3.68 (m, 1H), 3.16 (tt, $J = 11.35, 3.52$ Hz, 1H), 3.12-3.06 (m, 1H), 3.02-2.97 (m, 1H), 2.9-2.87 (m, 1.4H), 2.87-2.75 (m, 0.6H), 2.55-2.43 (m, 3H), 2.27-2.17 (m, 3H), 2.21 (s, 1.5H), 2.17 (s, 1.5H), 2.04-1.87 (m, 2H).

EXAMPLE 14



1-[1-{3-[4-(Benzo[d]isoxazol-3-yloxy)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-
5 trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

A. 4-(Benzo[d]isoxazol-3-yloxy)-piperidine-1-carboxylic acid tert-butyl ester.

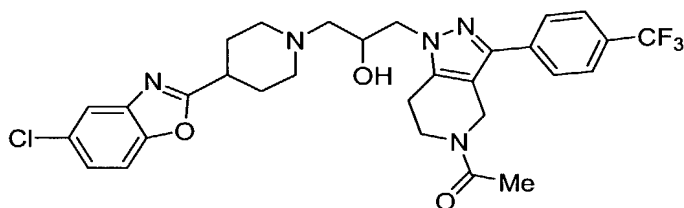
To a stirred solution of 263 mg of *t*-butyl-4-hydroxy-1-piperidinecarboxylate (1.3
10 mmol) in 5 mL of dry DMF was added 52 mg of 60% NaH in mineral oil (1.3
mmol). After stirring at room temperature for 10 min, 100 mg (0.65 mmol) of 3-
chloro-1,2-benzisoxazole in DMF (1 mL) was added. The mixture was stirred
at 40 °C overnight and then partitioned between EtOAc (50 mL) and water (20
mL) and separated. The aqueous layer was further extracted with EtOAc (2 x
15 30 mL). The combined organic layers were then washed with water (25 mL),
brine, dried over Na₂SO₄, and the solvent was removed under reduced
pressure to give crude product. Purification by chromatography (silica,
gradient elution of 40% hexanes/CH₂Cl₂ to 100%CH₂Cl₂) gave 176 mg (85%)
product as a light yellow solid. MS (electrospray): exact mass calculated for
20 C₁₇H₂₂N₂O₄, 318.16; *m/z* found, 341.1 [M+Na]⁺. ¹H NMR (CDCl₃, 400 MHz):
7.64 (dt, *J* = 8.02, 1.17 Hz, 1H), 7.53 (ddd, *J* = 8.41, 7.04, 1.17 Hz, 1H), 7.43
(dt, *J* = 8.41, 0.78 Hz, 1H), 7.27 (ddd, *J* = 8.02, 7.04, 0.78 Hz, 1H), 5.07 (m,
1H), 3.87-3.77 (br m, 2H), 3.30 (m, 2H), 2.17-2.10 (br m, 2H), 1.93-1.84 (br m,
2H), 1.48 (s, 9H).

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B. 1-[1-{3-[4-(Benzo[d]isoxazol-3-yloxy)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-
trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.
A solution of 176 mg (0.55 mmol) of 4-(benzo[d]isoxazol-3-yloxy)-piperidine-1-
carboxylic acid tert-butyl ester in CH₂Cl₂ (2 mL) was treated with trifluoroacetic

acid (0.5 mL) at room temperature overnight. The solvent was then removed and the crude product dissolved in methanol and stirred over 100 mg of sodium bicarbonate for 1 h, the solid was then filtered off and the filtrate concentrated. The crude piperidine was then dissolved in 4 mL EtOH and treated with 202 mg (0.55 mmol) of 1-[1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone. The solution was heated to 60 °C overnight. The solvent was then removed by rotary evaporation and the crude product was purified by column chromatography (silica, 0-10% MeOH/EtOAc) to afford 220 mg (68%) of a white solid. MS (electrospray): exact mass calculated for $C_{30}H_{32}F_3N_5O_4$, 583.24; m/z found, 584.2 $[M+H]^+$. 1H NMR ($CDCl_3$, 400 MHz, a mixture of amide rotamers): 7.77 (d, J = 8.22 Hz, 1H), 7.69 (m, 2H), 7.66-7.61 (m, 2H), 7.54-7.49 (m, 1H), 7.41 (d, J = 8.41 Hz, 1H), 7.28-7.23 (m, 1H), 4.93 (br m, 1H), 4.88 and 4.75 (A and B of AB quartet, J = 15.65 Hz, 1H), 4.65 (br s, 1H), 4.24-4.18 (m, 0.75H), 4.18-4.09 (m, 1.25H), 4.07-3.98 (m, 1.5H), 3.91-3.79 (m, 0.5H), 3.79-3.67 (m, 1H), 3.02-2.85 (m, 2.4H), 2.85-2.70 (m, 1.6H), 2.61-2.52 (m, 1H), 2.51-2.40 (m, 2H), 2.39-2.30 (m, 1H), 2.24-2.12 (br m, 2H), 2.20 (s, 1.5H), 2.16 (s, 1.5H), 2.02-1.86 (m, 2H).

EXAMPLE 15



1-[1-{3-[4-(5-Chloro-benzooxazol-2-yl)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

A. 5-Chloro-2-piperidin-4-yl-benzooxazole.

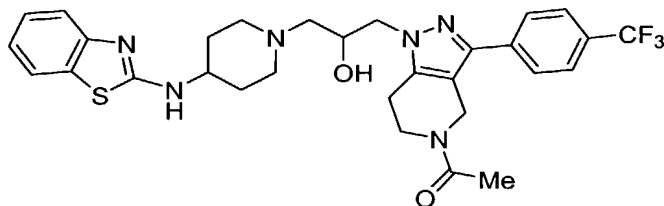
A flask was charged with 1.35 mL (10 mmol) of methyl isonipicotate, 1.43 g (10 mmol) of 2-amino-4-chlorophenol, and 5 g of polyphosphoric acid. The flask was then heated to 180 °C for 5 h. The reaction mixture was then poured into

water while still warm and treated with 50% KOH solution until pH 12. This was then extracted with CH₂Cl₂ (3 x 50 mL), then washed with water (25 mL), brine, dried over Na₂SO₄, and the solvent was removed under reduced pressure to give 1.53 g (57%) of crude product which was used without further purification. MS (electrospray): exact mass calculated for C₁₂H₁₃ClN₂O, 236.07; *m/z* found, 237.1 [M+H]⁺.

B. 1-[1-{3-[4-(5-Chloro-benzooxazol-2-yl)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

A solution of 130 mg (0.55 mmol) of 5-chloro-2-piperidin-4-yl-benzooxazole was dissolved in 4 mL EtOH and treated with 100 mg (0.27 mmol) of 1-[1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone. The solution was heated to 60 °C overnight. The solvent was then removed by rotary evaporation and the crude product was purified by column chromatography (silica, 0-10% MeOH/EtOAc) to afford 156 mg (95%) of a white solid. MS (electrospray): exact mass calculated for C₃₀H₃₁ClF₃N₅O₃, 601.21; *m/z* found, 602.2 [M+H]⁺. ¹H NMR (CDCl₃, 400 MHz, a mixture of amide rotamers): 7.76 (d, *J* = 8.41 Hz, 1H), 7.71 and 7.67 (A and B of AB quartet, *J* = 8.41 Hz, 2H), 7.65-7.61 (m, 2H), 7.38 (d, *J* = 8.61 Hz, 1H), 7.26 (dd, *J* = 8.61, 1.96, 1H), 4.86 and 4.74 (A and B of AB quartet, *J* = 15.65 Hz, 1H), 4.64 (br s, 1H), 4.24-4.10 (m, 2.3H), 4.07-3.97 (m, 1.7H), 3.89-3.67 (m, 2H), 3.06-3.00 (m, 1H), 3.00-2.90 (m, 2H), 2.90-2.74 (m, 2H), 2.51-2.38 (m, 3H), 2.25-2.10 (m, 2.3H), 2.20 (s, 1.5H), 2.15 (s, 1.5H), 2.06-1.83 (m, 2.7H).

EXAMPLE 16



1-[1-{3-[4-(Benzothiazol-2-ylamino)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

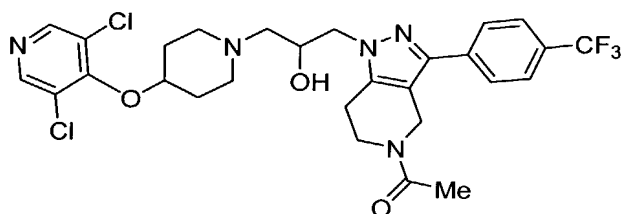
A. 4-(Benzothiazol-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester.

- 5 To a stirred solution of 300 mg (1.77 mmol) of 2-chlorobenzothiazole in dry DMF (3.5 mL) was added 2.9 g of cesium carbonate (8.8 mmol) and 535 mg of *tert*-butyl-4-hydroxy-1-piperidinecarboxylate (2.66 mmol). The mixture was stirred at room temperature for 4 h before it was partitioned between EtOAc (70 mL) and water (30 mL) and separated. The aqueous layer was further
- 10 extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with water (25 mL), brine, dried over Na₂SO₄, and the solvent was removed under reduced pressure. Purification by flash chromatography (silica, 0-15% EtOAc/hexanes) afforded 220 mg (37%) of the desired product as a white solid. MS (electrospray): exact mass calculated for C₁₇H₂₃N₃O₂S, 333.15; *m/z*
- 15 found, 334.2 [M+H]⁺. ¹H NMR (CDCl₃, 400 MHz): 7.65 (t, *J* = 7.63 2H), 7.36 (ddd, *J* = 8.41, 7.43, 1.37 Hz, 1H), 7.22 (dt, *J* = 7.63, 1.17 Hz, 1H), 5.36 (m, 1H), 3.79-3.70 (br m, 2H), 3.36 (m, 2H), 2.12-2.04 (br m, 2H), 1.92-1.82 (br m, 2H), 1.48 (s, 9H).

- 20 B. 1-[1-{3-[4-(Benzothiazol-2-ylamino)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone. A solution of 220 mg (0.66 mmol) of 4-(benzothiazol-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester in dichloromethane (2 mL) was treated with trifluoroacetic acid (0.5 mL) at room temperature overnight. The solvent was
- 25 then removed and the crude product dissolved in MeOH and stirred over 100 mg of sodium bicarbonate for 1 h. The solid was filtered off and the filtrate concentrated. The crude piperidine was then dissolved in 4 mL EtOH and treated with 220 mg (0.60 mmol) of 1-[1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone. The solution
- 30 was heated to 60 °C overnight. The solvent was then removed by rotary evaporation and the crude product was purified by column chromatography (silica, 0-10% MeOH/EtOAc) to afford 240 mg (66%) of a white solid. MS (electrospray): exact mass calculated for C₃₀H₃₃F₃N₆O₂S: 598.23; *m/z* found,

599.3 [M+H]⁺. ¹H NMR (CDCl₃, 400 MHz, a mixture of amide rotamers): 7.78 (d, *J* = 8.22 Hz, 1H), 7.72 and 7.68 (A and B of AB quartet, *J* = 8.41 Hz, 2H), 7.64 (d, *J* = 8.22 Hz, 1H), 7.56 (bd, *J* = 8.02 Hz, 1H), 7.51 (bd, *J* = 8.02 Hz, 1H), 7.29 (bd, *J* = 7.63 Hz, 1H), 7.08 (bt, *J* = 7.63 Hz, 1H), 5.29 (br s, 1H), 4.88 and 4.75 (A and B of AB quartet, *J* = 15.65 Hz, 1H), 4.65 (br s, 1H), 4.23-4.16 (m, 1H), 4.16-4.08 (m, 1H), 4.06-3.98 (m, 2H), 3.92-3.65 (m, 3H), 3.03-2.70 (m, 4H), 2.52-2.41 (m, 3H), 2.26-2.18 (m, 1H), 2.21 (s, 1.5H), 2.16 (s, 1.5H), 2.16-2.08 (m, 2H), 1.66-1.44 (m, 2H).

EXAMPLE 17



1-[1-{3-[4-(3,5-Dichloro-pyridin-4-yloxy)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

A. 4-(3,5-Dichloro-pyridin-4-yloxy)-piperidine-1-carboxylic acid tert-butyl ester.

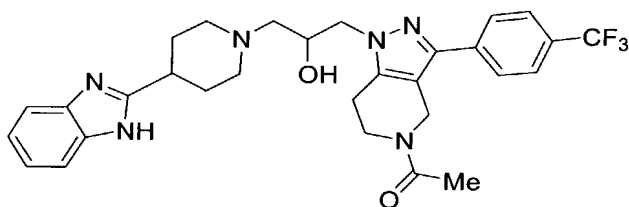
To a stirred solution of 828 mg (4.12 mmol) of *tert*-butyl-4-hydroxy-1-piperidinecarboxylate in 10 mL of dry DMF was added 165 mg of 60% NaH in mineral oil (4.12 mmol). After stirring at room temperature for 10 min, 500 mg (2.74 mmol) of 3,4,5-trichloropyridine was added. The mixture was stirred at 80 °C overnight and then partitioned between EtOAc (50 mL) and water (20 mL) and separated. The aqueous layer was further extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with water (25 mL), brine, dried over Na₂SO₄, and the solvent was removed under reduced pressure.

Column chromatography (silica, 60-100% CH₂Cl₂/hexanes) gave 265 mg (28%) of desired product. MS (electrospray): exact mass calculated for C₁₅H₂₀Cl₂N₂O₃, 346.09; *m/z* found, 369.1 [M+Na]⁺. ¹H NMR (CDCl₃, 400 MHz): 8.45 (s, 2H), 4.66 (m, 1H), 3.90-3.80 (br m, 2H), 3.26 (m, 2H), 1.96-1.83 (br m, 4H), 1.47 (s, 9H).

B. 1-[1-{3-[4-(3,5-Dichloro-pyridin-4-yloxy)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

- 5 A solution of 103 mg (0.30 mmol) of 4-(3,5-dichloro-pyridin-4-yloxy)-piperidine-1-carboxylic acid tert-butyl ester in CH_2Cl_2 (2 mL) was treated with trifluoroacetic acid (0.5 mL) at room temperature overnight. The solvent was then removed and the crude product dissolved in MeOH and stirred over 100 mg of sodium bicarbonate for 1 h. The solid was filtered off and the filtrate
- 10 concentrated. The crude piperidine was then dissolved in 4 mL EtOH and treated with 100 mg (0.27 mmol) of 1-[1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone. The solution was heated to 60 °C overnight. The solvent was then removed by rotary evaporation and the crude product was purified by column chromatography
- 15 (silica, 0-10% MeOH/EtOAc) to afford 90 mg (54%) of a white solid. MS (electrospray): exact mass calculated for $\text{C}_{28}\text{H}_{30}\text{Cl}_2\text{F}_3\text{N}_5\text{O}_3$, 611.17; m/z found, 612.2 $[\text{M}+\text{H}]^+$. ^1H NMR (CDCl_3 , 400 MHz, a mixture of amide rotamers): 8.44 (s, 2H), 7.77 (d, $J = 8.41$ Hz, 1H), 7.72 and 7.68 (A and B of AB quartet, $J = 8.41$ Hz, 2H), 7.65 (d, $J = 8.41$ Hz, 1H), 4.88 and 4.76 (A and B of AB quartet, $J = 15.65$ Hz, 1H), 4.66 (br s, 1H), 4.55 (br s, 1H), 4.26-4.08 (m, 2H), 4.08-3.98 (m, 2H), 3.91-3.69 (m, 2H), 3.03-2.92 (m, 1.6H), 2.91-2.85 (m, 0.8H), 2.85-2.75 (m, 1.6H), 2.52-2.40 (m, 3H), 2.35-2.24 (br m, 1H), 2.22 (s, 1.5H), 2.17 (s, 1.5H), 2.03-1.90 (m, 4H).
- 20

25 EXAMPLE 18



1-[1-{3-[4-(1H-Benzoimidazol-2-yl)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone.

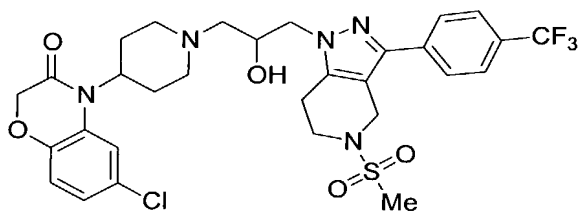
A. 2-Piperidin-4-yl-1H-benzoimidazole.

A flask was charged with 1.35 mL (10 mmol) of methyl isonipicotate, 1.0 g (10 mmol) of 1,2-phenylenediamine and 5 g of polyphosphoric acid. The flask was then heated to 180 °C for 5 h. The reaction mixture was then poured into water while still warm and treated with 50% KOH solution until pH 12. This was then extracted with CH₂Cl₂ (3 x 50 mL), washed with water (25 mL), brine, dried over Na₂SO₄, and the solvent was removed under reduced pressure to give 530 mg (27%) of crude product which was used without further purification. MS (electrospray): exact mass calculated for C₁₂H₁₅N₃, 201.13; *m/z* found, 202.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): 12.1 (br s, 1H), 7.49 (br m, 1H), 7.38 (br m, 1H), 7.09 (br m, 2H), 3.00 (dt, *J* = 12.13, 3.33 Hz, 2H), 2.88 (tt, *J* = 11.54, 3.74 Hz, 1H), 2.57 (dt, *J* = 12.13, 2.35 Hz, 2H), 1.90 (m, 2H), 1.66 (m, 2H).

B. 1-[1-{3-[4-(1H-Benzoimidazol-2-yl)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-*c*]pyridin-5-yl]-ethanone.

A solution of 83 mg (0.41 mmol) of 2-piperidin-4-yl-1H-benzoimidazole was dissolved in 4 mL EtOH and treated with 100 mg (0.27 mmol) of 1-[1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-*c*]pyridin-5-yl]-ethanone. The solution was heated to 60 °C overnight. The solvent was then removed by rotary evaporation and the crude product was purified by column chromatography (silica, 0-10% MeOH/EtOAc) to afford 55 mg (36%) of a white solid. MS (electrospray): exact mass calculated for C₃₀H₃₃F₃N₆O₂, 566.26; *m/z* found, 567.3 [M+H]⁺. ¹H NMR (CDCl₃, 400 MHz, a mixture of amide rotamers): 10.66 (br s, 0.5H), 10.57 (br s, 0.5H), 7.73 (bd, *J* = 8.41 Hz, 1H), 7.72-7.63 (m, 3H), 7.60 (bd, *J* = 8.41 Hz, 1H), 7.39-7.32 (m, 1H), 7.23-7.13 (m, 2H), 7.02 (br s, 1), 4.86 and 4.75 (A and B of AB quartet, *J* = 15.85 Hz, 1.25H), 4.64 (br s, 1H), 4.21-4.06 (m, 2H), 4.06-3.81 (m, 2H), 3.80-3.63 (m, 1H), 3.80-3.69 (m, 1H), 3.00-2.68 (m, 5H), 2.44-2.36 (m, 2H), 2.39-2.23 (m, 2H), 2.19 (s, 1.6H), 2.15 (s, 1.4H), 2.13-2.00 (m, 4H), 2.00-1.80 (m, 2H).

EXAMPLE 19



6-Chloro-4-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-
 5 4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-
 benzo[1,4]oxazin-3-one.

10 A. 5-Methanesulfonyl-1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-
tetrahydro-1H-pyrazolo[4,3-c]pyridine.

5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-
 pyrazolo[4,3-c]pyridine (10.0 g, 29.0 mmol) and epichlorohydrin (24 mL, 307
 mmol) were set stirring in DMF (150 mL) containing Cs₂CO₃ (10.4 g, 31.9
 mmol). After stirring at room temperature for 4 days the mixture was
 15 evaporated, brought up in EtOAc and washed with water. The organics were
 dried (MgSO₄) and evaporated to give a light yellow solid. Column
 chromatography (silica, 5% acetone/CH₂Cl₂) gave 4.1 g (35%) of a white solid.
 TLC (silica, 5% acetone/CH₂Cl₂): R_f = 0.28. MS (electrospray): exact mass
 calculated for C₁₇H₁₈F₃N₃O₃S, 401.10; *m/z* found, 402.1 [M+H]⁺. ¹H NMR (400
 20 MHz, CDCl₃); 7.84 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 4.70-4.62 (m,
 3H), 4.25 (d, *J* = 5.4 Hz, 1H), 3.90-3.70 (m, 2H), 3.47 (m, 1H), 3.10-2.9 (m,
 6H), 2.65-2.60 (m, 1H).

25 B. 4-(5-Chloro-2-hydroxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl
ester.

2-Amino-4-chloro-phenol (30.0 g, 209 mmol) and 4-oxo-piperidine-1-carboxylic
 acid tert-butyl ester (46.0 g, 231 mmol) were set stirring in dichloromethane
 (600 mL). Sodium triacetoxyborohydride (58.0 g, 274 mmol) was added in
 portions over 10 min. Acetic acid (12 mL, 210 mmol) was then added and the

mixture left to stir for 18 h. Saturated NaHCO_3 was added and the organics separated. The organics were dried (MgSO_4) and evaporated to give 56 g (82%) of a light beige solid. TLC (silica, 50% EtOAc/hexanes): R_f = 0.66. MS (electrospray): exact mass calculated for $\text{C}_{16}\text{H}_{23}\text{ClN}_2\text{O}_3$, 326.14; m/z found, 349.1 $[\text{M}+\text{Na}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 6.70 (d, J = 8.3 Hz, 1H), 6.63 (s, 1H), 6.47 (d, J = 8.2 Hz, 1H), 3.97 (d, J = 12.2 Hz, 2H), 3.55-3.50 (m, 1H), 2.93 (br s, 2H), 1.93 (d, J = 11.1 Hz, 2H), 1.48 (s, 9H), 1.35 (d, J = 11.2 Hz, 2H).

10 C. 4-[(5-Chloro-2-hydroxy-phenyl)-ethoxycarbonylmethyl-amino]-piperidine-1-carboxylic acid tert-butyl ester.

4-(5-Chloro-2-hydroxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (15.6 g, 47.7 mmol) was set stirring in THF (200 mL) and cooled to 5 °C. Sodium hydride (1.37 g, 54.2 mmol) was added in portions over 10 min and the mixture left to stir for 1 h. Ethyl bromoacetate (5.8 mL, 52.3 mmol) was added and the ice bath removed. After stirring for 20 h the mixture was evaporated, brought up in EtOAc and washed with water. The organics were dried (MgSO_4) and evaporated to give 22.5 g of a deep red oil. The oil was purified (silica, 5% acetone/ CH_2Cl_2) to give 12.9 g (65%) of a clear orange liquid. TLC (silica, 5% acetone/ CH_2Cl_2): R_f = 0.43. MS (electrospray): exact mass calculated for $\text{C}_{20}\text{H}_{29}\text{ClN}_2\text{O}_5$, 412.18; m/z found, 413.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): 6.75-6.62 (m, 3H), 4.71 (s, 1H), 4.37 (q, J = 7.2 Hz, 2H), 4.14 (br s, 2H), 3.55-3.50 (m, 1H), 3.08 (br t, 2H), 2.14 (m, 2H), 1.65-1.45 (m, 12H), 1.41 (t, J = 7.2 Hz, 3H).

25

D. 4-(6-Chloro-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-piperidine-1-carboxylic acid tert-butyl ester.

4-[(5-Chloro-2-hydroxy-phenyl)-ethoxycarbonylmethyl-amino]-piperidine-1-carboxylic acid tert-butyl ester (12.9 g, 31.2 mmol) was set stirring in MeOH (100 mL). A solution of NaOH (2.5 g, 62.5 mmol) in water (100 mL) was added and the mixture stirred at room temperature for 3 h. The mixture was acidified to pH 2 and MeOH evaporated. The aqueous layer was extracted twice with EtOAc. The organics were combined, dried (MgSO_4) and evaporated to give

11 g of a clear orange oil. The oil was set stirring in CH_2Cl_2 (150 mL) and EDC (8.2 g, 42.8 mmol) was added. After 1 h the organics were washed with 1 *N* HCl (100 mL), water (100 mL) and dried (MgSO_4). The solvent was evaporated to give 7.2 g (63%) of a clear orange solid. TLC (silica, 5% acetone/ CH_2Cl_2): R_f = 0.53. MS (electrospray): exact mass calculated for $\text{C}_{18}\text{H}_{23}\text{ClN}_2\text{O}_4$, 366.13; *m/z* found, 389.1 $[\text{M}+\text{Na}]^+$. ^1H NMR (400 MHz, CDCl_3): 7.19 (s, 1H), 7.11-7.00 (m, 2H), 4.60 (s, 2H), 4.50-4.30 (m, 3H), 3.00-2.80 (m, 2H), 2.70-2.60 (m, 2H), 1.86 (d, J = 11.4 Hz, 2H), 1.60 (s, 9H).

10 E. 6-Chloro-4-piperidin-4-yl-4H-benzo[1,4]oxazin-3-one.

4-(6-Chloro-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-piperidine-1-carboxylic acid tert-butyl ester (7.2 g, 19.6 mmol) was set stirring and a 1:1 TFA/ CH_2Cl_2 solvent mixture was added. After 1 h the mixture was evaporated under reduced pressure and the resulting red oil brought up in Et_2O . A solid formed and was filtered and air dried to give 7.2 g (96%) of a light beige solid. MS (electrospray): exact mass calculated for $\text{C}_{13}\text{H}_{15}\text{ClN}_2\text{O}_2$, 266.08; *m/z* found, 267.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CD_3OD): 7.52 (s, 1H), 7.20-7.00 (m, 2H), 4.60 (s, 2H), 4.50-4.40 (m, 1H), 3.65-3.55 (m, 2H), 3.28 (t, J = 13.1 Hz, 2H), 3.10-3.00 (m, 2H), 2.15 (d, J = 13.9 Hz, 2H).

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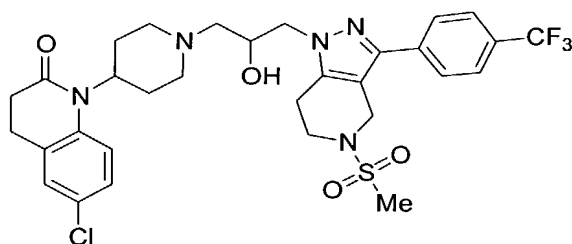
F. 6-Chloro-4-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-benzo[1,4]oxazin-3-one.

6-Chloro-4-piperidin-4-yl-4H-benzo[1,4]oxazin-3-one (252 mg, 0.66 mmol) and 5-methanesulfonyl-1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (209 mg, 0.52 mmol) were set stirring in EtOH (10 mL) containing Et_3N (115 μL , 0.83 mmol) at 70 $^\circ\text{C}$. After 2 days the mixture was cooled, evaporated, brought up in EtOAc and washed with saturated NaHCO_3 . The organics were dried (MgSO_4) and evaporated to give a clear golden oil. The oil was purified (silica, 50% acetone/ CH_2Cl_2) to give 191 mg (55%) of a white solid. TLC (silica, 50% acetone/ CH_2Cl_2): R_f = 0.38. MS (electrospray): exact mass calculated for $\text{C}_{30}\text{H}_{33}\text{ClF}_3\text{N}_5\text{O}_5\text{S}$, 667.18; *m/z* found,

668.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): 7.83 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.21 (s, 1H), 7.10-7.00 (m, 2H), 4.68 (d, J = 5.1 Hz, 2H), 4.58 (s, 2H), 4.40-4.10 (m, 4H), 3.90-3.70 (s, 2H), 3.30-3.0 (m, 4H), 3.00 (s, 3H), 2.90-2.70 (m, 2H), 2.65-2.50 (m, 3H), 2.35-2.20 (m, 2H), 1.88 (d, J = 11.3 Hz, 2H).

5

EXAMPLE 20



10 6-Chloro-1-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one.

A. 3-(2-Amino-5-chloro-phenyl)-acrylic acid ethyl ester.

15 2-Amino-5-chlorobenzaldehyde (7.58 g, 48.7 mmol) and 36 g (103 mmol) of (carbethoxymethylene)triphenylphosphorane were added in benzene (300 mL) and heated to reflux for 20 h. The reaction mixture was cooled and concentrated to give an orange oil. The oil was brought up in Et₂O and precipitated appeared. This was filtered and washed with Et₂O. The organics
20 were evaporated to give a clear orange oil. The oil was purified by column chromatography (silica, 10-40% EtOAc/hexanes) to obtain 10.4 g (95%) of a yellow solid. MS (electrospray): exact mass calculated for C₁₁H₁₂ClNO₂, 225.06; m/z found, 226.1 [M⁺+H]. ¹H NMR (400 MHz, CDCl₃): 7.69 (d, J = 15.85 Hz, 1H), 7.30 (d, J = 2.54 Hz, 1H), 7.07 (dd, J = 6.26 Hz, 2.35 Hz, 1H),
25 6.60 (d, J = 8.61 Hz, 1H), 6.30 (d, J = 15.85 Hz, 1H), 4.22 (dd, J = 7.24 Hz, 7.24 Hz, 2H), 3.98 (br s, 2H), 1.30 (t, J = 7.04 Hz, 3H).

B. 4-[4-Chloro-2-(2-ethoxycarbonyl-vinyl)-phenylamino]-piperidine-1-carboxylic acid tert-butyl ester.

3-(2-Amino-5-chloro-phenyl)-acrylic acid ethyl ester (10.4 g, 46 mmol) and 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (13.8 g, 69 mmol) were set stirring in CH_2Cl_2 (230 mL). Sodium triacetoxyborohydride (14.6 g, 69 mmol) was added in portions over 10 min. Acetic acid (1.3 mL, 25 mmol) was then added and the mixture left to stir. After 18 h saturated NaHCO_3 was added and the organics separated. The organics were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica, 20-50% EtOAc/hexanes) to obtain 12.4 g (66%) of a light beige solid. TLC (silica, 25% EtOAc/hexanes): R_f = 0.5. MS (electrospray): exact mass calculated for $\text{C}_{21}\text{H}_{29}\text{ClN}_2\text{O}_4$, 408.18; m/z found, 409.1 $[\text{M}^+ + \text{H}]$. ^1H NMR (400 MHz, CDCl_3): 7.64 (d, J = 15.65 Hz, 1H), 7.29 (d, J = 2.35 Hz, 1H), 7.14 (dd, J = 6.26 Hz, 2.54 Hz, 1H), 6.59 (d, J = 9.00 Hz, 1H), 6.28 (d, J = 15.65 Hz, 1H), 4.23 (dd, J = 7.04 Hz, 7.04 Hz, 2H), 4.11-3.98 (m, 2H), 3.81 (br s, 1H), 3.46-3.36 (m, 1H), 2.89 (t, J = 11.74 Hz, 2H), 2.04-1.95 (m, 2H), 1.44 (s, 9H), 1.42-1.33 (m, 2H), 1.30 (t, J = 7.24 Hz, 3H).

C. 4-[4-Chloro-2-(2-ethoxycarbonyl-ethyl)-phenylamino]-piperidine-1-carboxylic acid tert-butyl ester.

4-[4-Chloro-2-(2-ethoxycarbonyl-vinyl)-phenylamino]-piperidine-1-carboxylic acid tert-butyl ester (12.4 g, 30.4 mmol) in EtOAc (150 mL) containing PtO_2 (1 g) was placed on a Parr hydrogenator at 60 psi H_2 . After 18 h the mixture was filtered through celite and evaporated to give a clear brown liquid. The liquid was purified by column chromatography (silica, 20-50% EtOAc/hexanes) to obtain 5.7 g (46%) of the title compound. TLC (silica, 25% EtOAc/hexanes): R_f = 0.5. MS (electrospray): exact mass calculated for $\text{C}_{21}\text{H}_{31}\text{ClN}_2\text{O}_4$, 410.2; m/z found, 411.2 $[\text{M}^+ + \text{H}]$. ^1H NMR (400 MHz, CDCl_3): 7.05 (dd, J = 6.06 Hz, 2.54 Hz, 1H), 6.99 (d, J = 2.35 Hz, 1H), 6.55 (d, J = 8.61 Hz, 1H), 4.13 (dd, J = 7.04 Hz, 3.13 Hz, 2H), 4.11-3.98 (m, 2H), 3.81 (br s, 1H), 3.72 (t, J = 6.26 Hz, 2H), 3.46-3.36 (m, 1H), 2.75 (t, J = 7.43 Hz, 2H), 2.60 (t, J = 7.04, 2H), 2.04-1.95 (m, 2H), 1.46 (s, 9H), 1.42-1.33 (m, 2H), 1.26 (t, J = 7.24 Hz, 3H).

D. 4-[2-(2-Carboxy-ethyl)-4-chloro-phenylamino]-piperidine-1-carboxylic acid tert-butyl ester.

4-[4-Chloro-2-(2-ethoxycarbonyl-ethyl)-phenylamino]-piperidine-1-carboxylic acid tert-butyl ester (5.7 g, 13.9 mmol) was set stirring in MeOH (40 mL). A solution of NaOH (1.4 g, 34.7 mmol) in water (10 mL) was added and the mixture stirred at room temperature. After 3 h the mixture was acidified to pH 7 and MeOH was evaporated. The aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL). The organics were combined, dried over Na₂SO₄ and concentrated to afford 3.9 g (73%) of the desired product. TLC (silica, 50% EtOAc/hexanes): R_f = 0.4. MS (electrospray): exact mass calculated for C₁₉H₂₇ClN₂O₄, 382.17; m/z found, 381.1 [M-H].

E. 4-(6-Chloro-2-oxo-3,4-dihydro-2H-quinolin-1-yl)-piperidine-1-carboxylic acid tert-butyl ester.

4-[2-(2-Carboxy-ethyl)-4-chloro-phenylamino]-piperidine-1-carboxylic acid tert-butyl ester (3.9 g, 10.1 mmol) and EDC (2.9 g, 15.3 mmol) were set stirring in CH₂Cl₂ (50 mL) for 2 h. The reaction mixture was dissolved in CH₂Cl₂ (150 mL), washed with water (2 x 50 mL) and brine (1 x 50 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (silica, 30-50% EtOAc/hexanes) to obtain 1.9 g (52%) of the desired product. TLC (silica, 50% EtOAc/hexanes): R_f = 0.67. MS (electrospray): exact mass calculated for C₁₉H₂₅ClN₂O₃, 364.16; m/z found, 365.1 [M⁺+H]. ¹H NMR (400 MHz, CDCl₃): 7.14-7.08 (m, 2H), 6.98 (d, J = 8.61 Hz, 1H), 4.33-3.98 (m, 3H), 2.75 (t, J = 7.83 Hz, 4H), 2.55-2.36 (m, 4H), 1.70-1.65 (m, 2H), 1.44 (s, 9H).

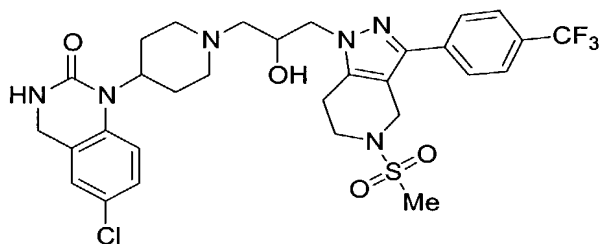
F. 6-Chloro-1-piperidin-4-yl-3,4-dihydro-1H-quinolin-2-one.

4-(6-Chloro-2-oxo-3,4-dihydro-2H-quinolin-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (1.2 g, 3.28 mmol) was set stirring in 1:1 TFA/CH₂Cl₂. After 45 min the mixture was evaporated and the golden oil brought up in Et₂O. A solid formed and was filtered, washed with Et₂O and air dried to give 1.3 g (93%) of a white solid. MS (electrospray): exact mass calculated for C₁₃H₁₇ClN₂O, 264.10; m/z found, 265.1 [M⁺+H].

G. 6-Chloro-1-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one.

- 5 6-Chloro-1-piperidin-4-yl-3,4-dihydro-1H-quinolin-2-one (270 mg, 0.62 mmol) and 5-methanesulfonyl-1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (165 mg, 0.41 mmol) were set stirring in EtOH (10 mL) containing Et₃N (97 μ L, 0.70 mmol) at 80 °C. After 16 h the mixture was cooled, evaporated, brought up in dichloromethane and washed
- 10 with water. The organics were dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (silica, 5-10% MeOH/CH₂Cl₂) to obtain 205 mg (75%) of a white solid. TLC (silica, 10% MeOH/CH₂Cl₂): R_f = 0.75. MS (electrospray): exact mass calculated for C₃₁H₃₅ClF₃N₅O₄S, 665.21; *m/z* found, 666.2 [M⁺+H]. ¹H NMR (CDCl₃, 400 MHz): 7.69 (d, *J* = 8.41 Hz, 2H), 7.62 (d, *J* = 8.41 Hz, 2H), 7.16-7.08 (m, 2H), 7.00 (d, *J* = 9.00 Hz, 1H), 4.52 (dd, *J* = 14.28 Hz, 5.48 Hz, 2H), 4.18 (dd, *J* = 10.56 Hz, 3.13 Hz, 1H), 4.14-4.04 (m, 2H), 4.03-3.96 (m, 1H), 3.72-3.56 (m, 2H), 3.10-2.96 (m, 2H), 2.95-2.86 (m, 2H), 2.85 (s, 3H), 2.75 (t, *J* = 6.26 Hz, 2H), 2.69-2.54 (m, 2H), 2.53-2.47 (m, 2H), 2.44-2.31 (m, 3H), 2.15-2.05 (m, 1H), 1.71-1.62 (m, 2H).
- 15
- 20

EXAMPLE 21



- 25 6-Chloro-1-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinazolin-2-one.

A. Spiro[piperidine-4,2'(1'H)-6'-chloro-3', 4'-dihydro-4'-oxo-quinazoline]-1-carboxylic acid tert-butyl ester.

To a stirred solution of 2-amino-5-chlorobenzamide (5.67 g, 33.2 mmol) and 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (6.62 g, 33.2 mmol) in benzene (70 mL) was added a catalytic amount (~0.3 g) of *p*-toluenesulfonic acid. The mixture was heated to reflux for 20 h under a Dean-Stark trap. The resulting suspension was concentrated. Saturated NaHCO₃ (68 mL) was added. The mixture was extracted with EtOAc and the precipitated crystals in the aqueous layer was collected by filtration. The solid was washed with water and dried to afford 11.22 g (96%) of the desired product. MS (electrospray): exact mass calculated for C₁₇H₂₂ClN₃O₃, 351.13; *m/z* found, 352.1 [M⁺+H]. ¹H NMR (CD₃OD, 400 MHz): 7.50 (d, *J* = 2.54 Hz, 1H), 7.13 (dd, *J* = 6.06 Hz, 2.54 Hz, 1H), 6.65 (d, *J* = 8.61 Hz, 1H), 3.56-3.47 (m, 2H), 3.36-3.25 (m, 2H), 1.79-1.66 (m, 4H), 1.32 (s, 9H).

B. 4-(2-Aminomethyl-4-chloro-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester.

Spiro[piperidine-4,2'(1'H)-6'-chloro-3', 4'-dihydro-4'-oxo-quinazoline]-1-carboxylic acid tert-butyl ester (1 g, 2.8 mmol) and borane-tetrahydrofuran complex (1.0 M, 9.9 mL, 9.9 mmol) were added in THF (10 mL) and heated to reflux for 6 h. The reaction mixture was cooled and poured into ice water. The resulting suspension was extracted with CH₂Cl₂ (2 x 100 mL). The organics were dried and concentrated. The residue was purified by column chromatography (silica, 5-10% MeOH/CH₂Cl₂) to obtain 795 mg (79%) of the product. MS (electrospray): exact mass calculated for C₁₇H₂₆ClN₃O₂, 339.17; *m/z* found, 362.1 [M⁺+Na]. ¹H NMR (CDCl₃, 400 MHz): 7.07 (dd, *J* = 6.06 Hz, 2.54 Hz, 1H), 6.97 (d, *J* = 2.54 Hz, 1H), 6.54 (d, *J* = 8.61 Hz, 1H), 3.94-3.70 (m, 4H), 3.48-3.38 (m, 1H), 3.05 (t, *J* = 11.15 Hz, 2H), 2.68-2.55 (m, 1H), 2.02-1.90 (m, 4H), 1.46 (s, 9H).

C. 4-(6-Chloro-2-oxo-3,4-dihydro-2H-quinazolin-1-yl)-piperidine-1-carboxylic acid tert-butyl ester.

1,1'-Carbonyldiimidazole (0.51 g, 3.15 mmol) was added to a solution of 4-(2-aminomethyl-4-chloro-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (0.79 g, 2.25 mmol) in CH₃CN (10 mL) over 3 h with stirring at 50 °C. The reaction mixture was then cooled to room temperature and stirred for additional 2 h. The reaction mixture was dissolved in CH₂Cl₂ (100 mL), washed with water (2 x 10 mL), brine (1 x 10 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (silica, 30-50% EtOAc/hexanes) to obtain 0.46 g (63%) of the desired product. TLC (silica, 50% EtOAc/hexanes): R_f = 0.5. MS (electrospray): exact mass calculated for C₁₈H₂₄ClN₃O₃, 365.15; *m/z* found, 388.1 [M⁺+Na]. ¹H NMR (CDCl₃, 400 MHz): 7.18 (dd, *J* = 6.26 Hz, 2.54 Hz, 1H), 7.05 (d, *J* = 2.15 Hz, 1H), 6.94 (d, *J* = 9.00 Hz, 1H), 6.29 (s, 1H), 4.32-4.18 (m, 4H), 4.13-4.02 (m, 1H), 2.88-2.71 (m, 2H), 2.64-2.50 (m, 2H), 1.82-1.73 (m, 2H), 1.49 (s, 9H).

D. 6-Chloro-1-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one.

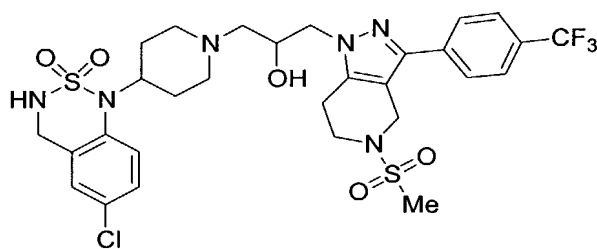
4-(6-Chloro-2-oxo-3,4-dihydro-2H-quinazolin-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (0.52 g, 1.42 mmol) was set stirring in 1:1 TFA/CH₂Cl₂. After 45 min the mixture was evaporated and the golden oil brought up in Et₂O. A solid formed and was filtered, washed with Et₂O and air dried to give 0.52 g (97%) of an off-white solid. MS (electrospray): exact mass calculated for C₁₃H₁₆ClN₃O, 265.10; *m/z* found, 266.1 [M⁺+H].

E. 6-Chloro-1-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinazolin-2-one.

6-Chloro-1-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (183 mg, 0.42 mmol) and 5-methanesulfonyl-1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (112 mg, 0.28 mmol) were set stirring in EtOH (10 mL) containing Et₃N (66 μL, 0.47 mmol) at 80 °C. After 16 h the mixture was cooled, evaporated, brought up in CH₂Cl₂ and washed with water. The organics were dried over Na₂SO₄ and concentrated. The residue was

purified by column chromatography (silica, 5-10% MeOH/CH₂Cl₂) to obtain 141 mg (76%) of a white solid. TLC (silica, 10% MeOH/CH₂Cl₂): R_f = 0.6. MS (electrospray): exact mass calculated for C₃₀H₃₄ClF₃N₆O₄S, 666.20; *m/z* found, 667.2 [M⁺+H]. ¹H NMR (CDCl₃, 400 MHz): 7.70 (d, *J* = 7.83 Hz, 2H), 7.63 (d, *J* = 8.02 Hz, 2H), 7.12 (dd, *J* = 6.65 Hz, 2.35 Hz, 1H), 7.01 (br s, 1H), 6.92 (d, *J* = 9.00 Hz, 1H), 5.44 (br s, 1H), 4.54 (dd, *J* = 14.67 Hz, 6.46 Hz, 2H), 4.23-4.08 (m, 4H), 4.05-3.97 (m, 1H), 3.92-3.80 (m, 1H), 3.74-3.57 (m, 2H), 3.14-2.99 (m, 2H), 2.97-2.87 (m, 2H), 2.86 (s, 3H), 2.78-2.57 (m, 2H), 2.48-2.32 (m, 3H), 2.10 (t, *J* = 11.50 Hz 1H), 1.80-1.70 (m, 2H).

EXAMPLE 22



1-[4-(6-Chloro-2,2-dioxo-3,4-dihydro-2H-2λ⁶-benzo[1,2,6]thiadiazin-1-yl)-piperidin-1-yl]-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propan-2-ol.

A. 4-(6-Chloro-2,2-dioxo-3,4-dihydro-2H-2λ⁶-benzo[1,2,6]thiadiazin-1-yl)-piperidine-1-carboxylic acid tert-butyl ester.

A solution of 4-(2-aminomethyl-4-chloro-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (678 mg, 2 mmol) and sulfamide (596 mg, 6.2 mmol) in pyridine (12 mL) was heated to reflux for 6 h. The reaction mixture was then cooled to room temperature and poured into ice water (50 mL). The solution was extracted with CH₂Cl₂ (4 x 100 mL). The organic extracts was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (silica, 30-50% EtOAc/hexanes) to obtain 767 mg (96%) of the desired product. TLC (silica, 50% EtOAc/hexanes): R_f = 0.75. MS (electrospray): exact mass calculated for C₁₇H₂₄ClN₃O₄S, 401.12; *m/z* found,

400.1 [M⁺-H]. ¹H NMR (CDCl₃, 400 MHz): 7.13 (dd, *J* = 6.46 Hz, 2.15 Hz, 1H), 7.00 (d, *J* = 1.96 Hz, 1H), 6.92 (d, *J* = 8.60 Hz, 1H), 5.54 (br s, 1H), 4.35 (s, 2H), 4.11-3.81 (m, 3H), 2.62 (br s, 2H), 1.90-1.66 (m, 4H), 1.34 (s, 9H).

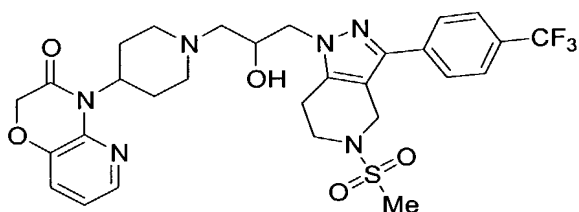
5 B. 6-Chloro-1-piperidin-4-yl-3,4-dihydro-1H-benzo[1,2,6]thiadiazine 2,2-dioxide.

4-(6-Chloro-2,2-dioxo-3,4-dihydro-2H-2l6-benzo[1,2,6]thiadiazin-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (767 mg, 1.91 mmol) was set stirring in 1:1 TFA/CH₂Cl₂. After 45 min the mixture was evaporated and the
10 golden oil brought up in Et₂O. A solid formed and was filtered, washed with Et₂O and air dried to give 730 mg (91%) of an off-white solid. MS (electrospray): exact mass calculated for C₁₂H₁₆ClN₃O₂S, 301.07; *m/z* found, 302.0 [M⁺+H].

15 C. 1-[4-(6-Chloro-2,2-dioxo-3,4-dihydro-2H-2λ⁶-benzo[1,2,6]thiadiazin-1-yl)-piperidin-1-yl]-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propan-2-ol.

6-Chloro-1-piperidin-4-yl-3,4-dihydro-1H-benzo[1,2,6]thiadiazine 2,2-dioxide (440 mg, 1.03 mmol) and 5-methanesulfonyl-1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (415 mg, 1.03 mmol) were set stirring in EtOH (20 mL) containing Et₃N (215 μL, 1.54 mmol) at 80 °C. After 16 h the mixture was cooled, evaporated, brought up in CH₂Cl₂ and washed with water. The organics were dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (silica, 0-
20 5% MeOH/CH₂Cl₂) to obtain 229 mg (32%) of a white solid. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.8. MS (electrospray): exact mass calculated for C₂₉H₃₄ClF₃N₆O₅S₂, 702.17; *m/z* found, 703.2 [M⁺+H]. ¹H NMR (CDCl₃, 400 MHz, a mixture of two rotamers): 7.66 (d, *J* = 8.61 Hz, 2H), 7.60 (d, *J* = 8.61 Hz, 2H), 7.16 (dd, *J* = 6.85 Hz, 1.96 Hz, 1H), 6.98 (s, 1H), 6.95 (d, *J* = 9.00 Hz, 1H), 4.47 (s, 2H), 4.33 (s, 2H), 4.16-3.99 (m, 2H), 3.98-3.90 (m, 1H), 3.89-3.78 (m, 1H), 3.62-3.52 (m, 2H), 3.05-2.95 (m, 1H), 2.93-2.84 (m, 2H), 2.82 (s, 3H), 2.81-2.76 (m, 1H), 2.33 (d, *J* = 6.46 Hz, 2H), 2.25 (t, *J* = 11.24 Hz, 1H), 2.09-1.90 (m, 3H), 1.90-1.78 (m, 2H).

EXAMPLE 23



- 5 4-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-pyrido[3,2-b][1,4]oxazin-3-one.
- 10 A. 4-(3-Hydroxy-pyridin-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester.
 To a stirring solution of 4.7 g (0.042 mol) of 2-amino-3-hydroxypyridine and 12.75 g (0.064 mol) of 4-oxo-piperidine-1-carboxylic acid tert-butyl ester in $\text{CH}_2\text{Cl}_2/\text{AcOH}$ (150 mL/60 mL) was added 10 g (0.070 mol) of Na_2SO_4 . After 3.5 h, 9.9 g (0.047) of sodium triacetoxyborohydride was added in three
 15 portions, and the mixture was stirred at room temperature for 15 h. The reaction was then quenched with NaHCO_3 (150 mL), extracted with CH_2Cl_2 (500 mL), washed with NaHCO_3 (2 x 100 mL), and the combined aqueous layers were extracted with EtOAc (150 mL). The combined organic layers were dried over Na_2SO_4 , concentrated, and purified using flash
 20 chromatography (silica, 3-10% MeOH/ CH_2Cl_2) to afford 5.9 g (48%) of a beige powder. MS (electrospray): exact mass calculated for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_3$, 293.17; m/z found, 294.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): 7.52 (dd, $J = 5.3$ Hz, 1.3 Hz, 1H), 6.79 (dd, $J = 7.6$ Hz, 1.3 Hz, 1H), 6.40 (dd, $J = 7.6$ Hz, 5.3 Hz, 1H), 4.06-3.94 (m, 3H), 3.02-2.86 (m, 2H), 2.72 (br s, 1H), 2.06-1.97 (m, 2H), 1.42 (s, 9H), 1.46-1.28 (m, 2H).
 25

B. 4-(3-Ethoxycarbonylmethoxy-pyridin-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester.

A stirring solution of 1.4 g (0.0048 mol) of 4-(3-hydroxy-pyridin-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester was dissolved in THF (24 mL) was
 5 cooled to 0 °C, and 0.13 g (0.0052 mol) of NaH was added. After 30 min, 0.8 g (0.0052 mol) of ethyl bromoacetate was added, and reaction was allowed to warm to room temperature and stirred overnight. Saturated NaHCO₃ (20 mL) was added and the reaction mixture was partitioned between EtOAc (200 mL) and saturated NaHCO₃ (75 mL). The organic layer was washed with water (50
 10 mL) and NaCl (50 mL), dried over Na₂SO₄, and concentrated to afford 0.9 g (49%) of a white powder. MS (electrospray): exact mass calculated for C₁₉H₂₉N₃O₅, 379.21; *m/z* found, 380.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): 7.74 (d, *J* = 5.3 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.46 (dd, *J* = 7.8 Hz, 5.3 Hz, 1H), 5.05 (d, *J* = 7.33 Hz, 1H), 4.59 (s, 2H), 4.26 (q, *J* = 7.3 Hz, 2H), 4.18-3.92 (m, 3H), 2.97 (t, *J* = 11.6 Hz, 2H), 2.06 (d, *J* = 12.1 Hz, 2H), 1.46 (s, 9H), 1.46-1.34 (m, 2H) 1.29 (t, *J* = 7.3 Hz, 3H).
 15

C. 4-(3-Oxo-2,3-dihydro-pyrido[3,2-b][1,4]oxazin-4-yl)-piperidine-1-carboxylic acid tert-butyl ester.

20 To a stirring solution of 0.9 g (0.0023 mol) of 4-(3-ethoxycarbonylmethoxy-pyridin-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester in H₂O/MeOH (1 mL/11 mL) was added 0.05 g (0.0023 mol) of LiOH. After 6 h, the solvent was removed under reduced pressure. The residue was dissolved in DMF (12 mL) and to the stirring solution was added 1.82 g (0.0048 mol) of HATU. After 3 h,
 25 the reaction was partitioned between EtOAc (250 mL) and saturated NaHCO₃ (100 mL), and washed with water (3 x 100 mL). The combined aqueous layers were extracted with EtOAc (100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, and concentrated to afford 0.37 g (46%) of a white solid. MS (electrospray): exact mass calculated for
 30 C₁₇H₂₃N₃O₄, 333.17; *m/z* found, 356.1 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃): 7.97 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.25 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 6.96 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 5.03 (tt, *J* = 11.9 Hz, 4.0 Hz, 1H), 4.55 (s, 2H), 4.13 (d, *J*

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= 10.9 Hz, 2H), 2.82-2.69 (m, 2H), 2.68 (qd, J = 12.4 Hz, 4.0 Hz, 2H), 1.65 (d, J = 12.1 Hz, 2H), 1.46 (s, 9H).

D. 4-Piperidin-4-yl-4H-pyrido[3,2-b][1,4]oxazin-3-one.

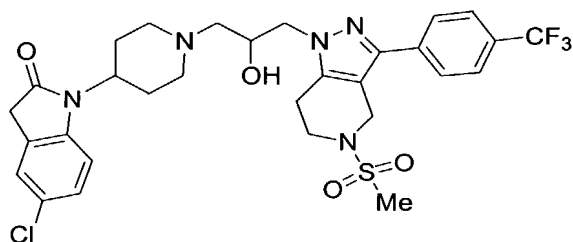
5 To a stirring solution of 0.37 g (0.0011 mol) of 4-(3-oxo-2,3-dihydro-pyrido[3,2-b][1,4]oxazin-4-yl)-piperidine-1-carboxylic acid tert-butyl ester in CH_2Cl_2 (2.5 mL) was added 2.5 mL of TFA. After 2.5 h, the solvent was removed. The residue was partitioned between EtOAc (200 mL) and 1 N NaOH (150 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined
10 organic layers were dried over Na_2SO_4 , and concentrated to afford 0.24 g (94%) of a white/pink solid. ^1H NMR (400 MHz, CDCl_3): 7.87 (dd, J = 4.8 Hz, 1.5 Hz, 1H), 7.25 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 6.84 (dd, J = 7.8 Hz, 4.8 Hz, 1H), 4.98-4.83 (m, 1H), 4.45 (s, 2H), 3.90 (s, 1H), 3.06 (d, J = 8.3 Hz, 2H), 2.65-2.53 (m, 4H), 1.65-1.53 (m, 2H).

15

E. 4-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-pyrido[3,2-b][1,4]oxazin-3-one.

To a stirring solution of 0.24 g (0.001 mol) of 4-piperidin-4-yl-4H-pyrido[3,2-b][1,4]oxazin-3-one in EtOH/Dichloroethane (2 mL/ 2 mL) was added 0.27 g (0.0007 mol) of 5-methanesulfonyl-1-oxiranymethyl-3-(4-trifluoro-methyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine. The reaction mixture was heated to 80 °C and stirred for 16 h. The solvent was then removed under reduced pressure, and the crude product was purified using flash
25 chromatography (30% acetone/ CH_2Cl_2), affording 0.42 g (96%) of a white solid. MS (electrospray): exact mass calculated for $\text{C}_{29}\text{H}_{33}\text{F}_3\text{N}_6\text{O}_5\text{S}$, 634.22; m/z found, 635.3 $[\text{M}+\text{H}]^+$. ^1H -NMR (400 MHz, CDCl_3): 8.00 (dd, J = 4.8 Hz, 1.5 Hz, 1H), 7.71 and 7.67 (A and B of AA'BB' quartet, J_{ab} = 8.4 Hz, 4H), 7.22 (dd, J = 7.9 Hz, 1.5 Hz, 1H), 6.94 (dd, J = 7.9 Hz, 4.8 Hz, 1H), 4.94 (tt, J = 12.1 Hz, 4.0 Hz, 1H) 4.57 and 4.55 (A and B of AB quartet, J_{ab} = 14.5 Hz, 2H), 4.57 (s, 2H),
30 4.25-4.02 (m, 3H), 3.78-3.61 (m, 2H), 3.16-2.90 (m, 4H), 2.90 (s, 3H), 2.89-2.76 (m, 1H), 2.56-2.43 (m, 3H) 2.23 (t, J = 11.2 Hz, 1H), 1.67 (d, J = 11.3 Hz, 2H).

EXAMPLE 24



- 5 5-Chloro-1-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one.

10 A. 2-(5-Chloro-2-nitro-phenyl)-malonic acid diethyl ester.

Sodium hydride (2.94 g, 123 mmol) was set stirring in DMSO (100 mL) and heated to 100 °C. Diethyl malonate (17.5 mL, 115 mmol) in DMSO (30 mL) was added and after 10 min a clear red solution was obtained. 2,4-Dichloronitrobenzene in DMSO (50 mL) was added. After 1.5 h the mixture was cooled and added to water (1000 mL). The product was extracted with ether. The organics were dried (MgSO₄) and evaporated to a clear yellow oil (10 g, 59%). TLC (silica, 20% EtOAc/hexanes): R_f = 0.36. MS (electrospray): exact mass calculated for C₁₃H₁₄ClNO₆, 315.05; *m/z* found, 338.0 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃): 8.05 (d, *J* = 8.7 Hz, 1H), 7.55-7.40 (m, 2H), 5.30 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 4H), 1.31 (t, *J* = 7.1 Hz, 6H).

B. (5-Chloro-2-nitro-phenyl)-acetic acid ethyl ester.

2-(5-Chloro-2-nitro-phenyl)-malonic acid diethyl ester (10.3 g, 32.6 mmol) in DMSO (200 mL) containing LiCl (2.9 g, 68.4 mmol) and water (0.6 mL, 33.3 mmol) was set stirring and heated to 100 °C. After 5 h the mixture was cooled to room temperature and added to water (750 mL). The product was extracted with two portions of EtOAc. The organics were combined, washed with water, dried (MgSO₄) and evaporated to give 5.9 g (75%) of a clear yellow oil. TLC (silica, 25% EtOAc /hexanes): R_f = 0.50. ¹H NMR (400 MHz, CDCl₃): 8.21 (d, *J*

= 8.8 Hz, 1H), 7.56 (dd, J = 8.8, 2.3 Hz, 2H), 7.47 (d, J = 2.3 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 4.12 (s, 2H), 1.38 (t, J = 7.1 Hz, 3H).

C. (2-Amino-5-chloro-phenyl)-acetic acid ethyl ester.

- 5 (5-Chloro-2-nitro-phenyl)-acetic acid ethyl ester (5.9 g, 24.2 mmol) in benzene (125 mL) containing PtO_2 (500 mg) was placed on a Parr hydrogenator at 40 psi H_2 . After 18 h the mixture was filtered through celite and evaporated to give a clear brown liquid. The liquid was purified (silica, 25% EtOAc/hexanes) to give 3.3 g (64%) of a clear golden liquid. TLC (silica, 25% EtOAc/hexanes): R_f
- 10 = 0.30. MS (electrospray): exact mass calculated for $\text{C}_{10}\text{H}_{12}\text{ClNO}_2$, 213.06; m/z found, 214.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): 7.20-7.10 (m, 2H), 6.78 (d, J = 8.3 Hz, 1H), 4.26 (q, J = 7.2, 2H), 1.18 (t, J = 7.1 Hz, 3H).

- 15 D. 4-(5-Chloro-2-oxo-2,3-dihydro-indol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester.

- (2-Amino-5-chloro-phenyl)-acetic acid ethyl ester (3.3 g, 15.4 mmol), 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (4.6 g, 23 mmol) were set stirring in CH_2Cl_2 (50 mL) and sodium triacetoxyborohydride (4.9 g, 23.1 mmol) was added followed by acetic acid (3 mL). After 5 days saturated NaHCO_3 was
- 20 added and the organics separated. The organics were dried (MgSO_4) and evaporated to give 7.5 g of a clear golden oil. The oil was purified (silica, 50% EtOAc/hexanes) to give 3.4 g (63%) of a white solid. TLC (silica, 25% EtOAc/hexanes): R_f = 0.18. MS (electrospray): exact mass calculated for $\text{C}_{18}\text{H}_{23}\text{ClN}_2\text{O}_3$, 350.14; m/z found, 373.1 $[\text{M}+\text{Na}]^+$. ^1H NMR (400 MHz, CDCl_3):
- 25 7.40-7.30 (m, 2H), 7.00 (d, J = 8.4 Hz, 1H), 4.55-4.45 (m, 1H), 4.40 (m, 2H), 3.63 (s, 2H), 2.94 (m, 2H), 2.45-2.30 (m, 2H), 1.82 (m, 2H), 1.62 (s, 9H).

E. 5-Chloro-1-piperidin-4-yl-1,3-dihydro-indol-2-one.

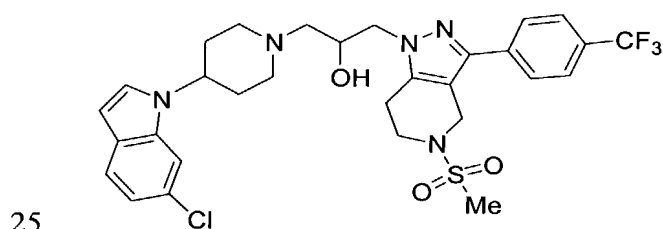
- 30 4-(5-Chloro-2-oxo-2,3-dihydro-indol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (3.4 g, 9.7 mmol) was set stirring in 1:1 TFA/ CH_2Cl_2 . After 45 min the mixture was evaporated and the golden oil brought up in Et_2O . A solid formed and was filtered, washed with Et_2O and air dried to give 3.4 g (97%) of a white solid. MS (electrospray): exact mass calculated for $\text{C}_{13}\text{H}_{15}\text{ClN}_2\text{O}$, 250.09; m/z

found, 251.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): 7.45 (s, 2H), 7.31 (d, *J* = 8.1 Hz, 1H), 4.55-4.45 (m, 1H), 3.68 (s, 2H), 3.50 (d, *J* = 12.3, 2H), 3.14 (m, 2H), 2.70-2.55 (m, 2H), 1.87 (d, *J* = 13.1 Hz, 2H).

5 F. 5-Chloro-1-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-
4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-
dihydro-indol-2-one.

5-Chloro-1-piperidin-4-yl-1,3-dihydro-indol-2-one (256 mg, 0.70 mmol) and 5-methanesulfonyl-1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (255 mg, 0.64 mmol) were set stirring in EtOH (15 mL) containing Et₃N (107 L, 0.77 mmol) at 80 °C. After 20 h the mixture was cooled, evaporated, brought up in CH₂Cl₂ and washed with water. The organics were dried (MgSO₄) and evaporated to give a clear golden oil. The oil was purified (silica, 50% acetone/CH₂Cl₂) to give 225 mg (54%) of a white solid. TLC (silica, 50% acetone/CH₂Cl₂): R_f = 0.32. MS (electrospray): exact mass calculated for C₃₀H₃₃ClF₃N₅O₄S, 651.19; *m/z* found, 652.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): 7.82 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.40-7.25 (m, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 4.66 (d, *J* = 4.0 Hz, 2H), 4.40-4.10 (m, 4H), 4.05-3.70 (m, 3H), 3.59 (s, 2H), 3.30-3.0 (m, 4H), 2.99 (s, 3H), 2.70-2.40 (m, 5H), 2.28 (m, 2H).

EXAMPLE 25



1-[4-(6-Chloro-indol-1-yl)-piperidin-1-yl]-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propan-2-ol.

A. 5-Chloro-2-(2,2-dimethoxy-ethyl)-phenylamine.

To a stirred solution of 10.3 g (60 mmol) of 4-chloro-2-nitrotoluene in dry DMF (120 mL) was added 16.45 g of N,N-dimethylformamide dimethylacetal (138 mmol). The mixture was heated to 140 °C for 18 h after which the solvent was removed under reduced pressure and the residue diluted with 150 mL of MeOH and 15.2 mL of chlorotrimethylsilane (120 mmol). The reaction mixture was then heated to 60 °C overnight. Methanol was then removed under reduced pressure and the residue was taken up in EtOH and transferred to a Parr bottle. 100 mg of 10% Platinum on carbon was added and the reaction mixture was put under 2 atmospheres of hydrogen on a Parr shaker for 8 h. When the reaction was completed the catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The crude aniline was used without further purification. TLC (silica, 35% EtOAc/hexanes): R_f = 0.4. MS (electrospray): exact mass calculated for $C_{10}H_{14}ClNO_2$, 215.07; m/z found, 216.1 $[M+H]^+$.

B. 4-[5-Chloro-2-(2,2-dimethoxy-ethyl)-phenylamino]-piperidine-1-carboxylic acid tert-butyl ester.

To a stirred solution of 2 g of 5-chloro-2-(2,2-dimethoxy-ethyl)-phenylamine, (9.27 mmol) in 50 mL of acetic acid was added 3.7 g of 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (18.5 mmol). The reaction mixture was allowed to stir for 1 h at room temperature before the portion wise addition of 5.9 g of sodium triacetoxyborohydride (27.9 mmol). The reaction mixture was allowed to stir an additional 5 h before removing the solvent under reduced pressure. The crude product was partitioned between CH_2Cl_2 (250 mL) and water. The aqueous layer was further extracted with CH_2Cl_2 (2 x 75 mL). The combined organic layers were then washed with 1 N NaOH (2 x 50 mL), brine, dried over Na_2SO_4 , and concentrated. Purification by chromatography (silica, 10-25% EtOAc/hexanes) afforded 1.5 g (71%) of desired product. TLC (silica, 35% EtOAc/hexanes): R_f = 0.49. MS (electrospray): exact mass calculated for $C_{20}H_{31}ClN_2O_4$, 398.20; m/z found, 399.2 $[M+H]^+$. 1H NMR ($CDCl_3$, 400 MHz): 6.94 (d, J = 7.83 Hz, 1H), 6.61 (dd, J = 7.83, 2.02 Hz, 1H), 6.57 (d, J = 2.02 Hz,

1H), 4.87 (br s, 1H), 4.40 (t, $J = 5.31$ Hz, 1H), 3.97 (br m, 2H), 3.36 (s, 6H), 3.02 (m, 2H), 2.78 (d, $J = 5.05$ Hz, 2H), 2.00 (m, 2H), 1.47 (s, 9H), 1.37 (m, 2H).

5 C. 6-Chloro-1-piperidin-4-yl-1H-indole.

To a stirred solution of 1.03 g (2.59 mmol) of 4-[5-chloro-2-(2,2-dimethoxyethyl)-phenylamino]-piperidine-1-carboxylic acid tert-butyl ester in 15 mL toluene was added 1.0 g (5.2 mmol) of *p*-toluenesulfonic acid. The reaction mixture was heated to 60 °C for 20 min, allowed to cool to room temperature and quenched with 100 mL of sat. aqueous NaHCO₃ then extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to afford 590 mg (98%) of the desired product as a pink oil. MS (electrospray): exact mass calculated for C₁₃H₁₅ClN₂, 234.09; m/z found, 235.1 [M+H]⁺. ¹H NMR (CDCl₃, 400 MHz, a mixture of amide rotamers): 7.52 (d, $J = 8.34$ Hz, 1H), 7.38 (br s, 1H), 7.21 (d, $J = 3.28$ Hz, 1H), 7.06 (dd, $J = 8.34, 1.77$ Hz, 1H), 6.49 (d, $J = 3.28$ Hz, 1H), 4.24 (m, 1H), 3.30 (m, 2H), 2.85 (dt, $J = 12.38, 2.53$ Hz, 2H), 2.08 (m, 2H), 1.94 (m, 2H).

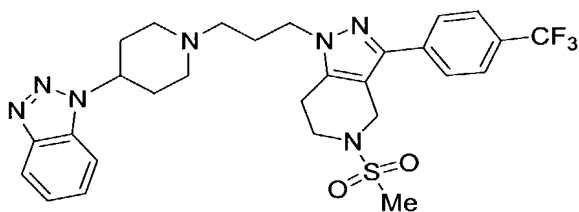
20 D. 1-[4-(6-Chloro-indol-1-yl)-piperidin-1-yl]-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propan-2-ol.

To a stirred solution of 86 mg (0.21 mmol) of 5-methanesulfonyl-1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine in 4 mL of EtOH was added 50 mg (0.39 mmol) of 6-chloro-1-piperidin-4-yl-1H-indole. The solution was heated to 60 °C overnight. The solvent was then removed by rotary evaporation and the crude product was purified by column chromatography (silica, gradient elution from 0-5% 2 *N* NH₃/MeOH in CH₂Cl₂) to afford 64 mg (48%) of a white solid. MS (electrospray), exact mass calculated for C₃₀H₃₃ClF₃N₅O₃S: 635.19; m/z found, 636.2 [M+H]⁺. HPLC (reverse phase conditions 10-90%), $t_R = 4.88$ min. ¹H NMR (CDCl₃, 400 MHz): 7.72 and 7.67 (A and B of AB quartet, $J = 8.80$ Hz, 4H), 7.52 (d, $J = 8.41$, 1H), 7.34 (s, 1H), 7.18 (d, $J = 3.33$ Hz, 1H), 7.07 (dd, $J = 8.41, 1.76$ Hz, 1H), 6.50 (d, $J = 3.33$ Hz, 1H), 4.59 and 4.54 (A and B of AB

quartet, $J = 14.48$ Hz, 2H), 4.24 (dd, $J = 13.69$, 2.39 Hz, 1H), 4.21-4.14 (m, 2H), 4.05 (dd, $J = 13.69$, 6.46 Hz, 1H), 3.69 (m, 2H), 3.15 (br d, $J = 11.54$ Hz, 1H), 3.11-2.91 (m, 3H), 2.60-2.48 (m, 3H), 2.28 (dt, $J = 11.74$, 2.15 Hz, 1H), 2.13-1.93 (m, 4H).

5

EXAMPLE 26



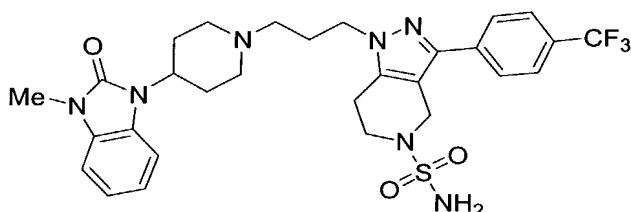
10 1-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1H-benzotriazole.

To a stirred solution of 3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propionaldehyde (0.084 g, 0.21 mmol) in CH_2Cl_2 (0.5 mL) were added 1-piperidin-4-yl-1H-benzotriazole hydrochloride (Maybridge Chemicals, 0.050 g, 0.21 mmol), Et_3N (0.1 mL) and glacial AcOH (12 mL, 0.21 mmol) in that order and stirred for 20 min. $\text{NaBH}(\text{OAc})_3$ (0.058 g, 0.27 mmol) was added and stirred under nitrogen overnight. Saturated NaHCO_3 (1 mL) was added and stirred for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 mL). The combined organic extracts were washed with brine (3 mL), dried over Na_2SO_4 , and removed under reduced pressure. MPLC of the crude afforded the desired compound as a white solid (0.098 g, 80 %). TLC (silica, 12% MeOH/ CH_2Cl_2): $R_f = 0.44$. MS (electrospray): exact mass calculated for $\text{C}_{28}\text{H}_{32}\text{F}_3\text{N}_7\text{O}_2\text{S}$, 587.23; m/z found 588.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): 8.00 (d, $J = 8.4$ Hz, 1H), 7.66 (d, $J = 8.2$ Hz, 2H), 7.59 (d, $J = 8.2$ Hz, 2H), 7.50 (d, $J = 8.4$ Hz, 1H), 7.41 (dt, $J = 0.9$, 7.6 Hz, 1H), 7.30 (dt, $J = 0.9$, 7.6 Hz, 1H), 4.59 (br t, $J = 11.2$ Hz, 1H), 4.50 (s, 2H), 4.10 (t, $J = 6.7$ Hz, 2H), 3.63 (t, $J =$

5.8 Hz, 2H), 3.00 (br d, J = 12.0 Hz, 2H), 2.89 (t, J = 5.8 Hz, 2H), 2.86 (s, 3H), 2.38-2.27 (m, 4H), 2.17-1.99 (m, 6H).

EXAMPLE 27

5



1-{3-[4-(3-Methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-sulfonic acid amide.

10

A. 1-(3-Oxo-propyl)-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester.

Dess-Martin periodinane (1.43 g, 3.36 mmol) was added portion wise to a stirred solution of 1-(3-hydroxy-propyl)-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (1.30 g, 3.05 mmol) in CH_2Cl_2 (15 mL) at 0 °C under N_2 . Then the reaction was stirred at 0 °C for 15 min and allowed to warm to room temperature. After stirring at room temperature for 1.5 h the reaction was diluted with Et_2O (50 mL) and saturated NaHCO_3 (15 mL) was added slowly (caution! gas evolution). Then $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ (5.31 g, 21.4 mmol) was added and stirred for 30 min. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 30 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. MPLC (1-10% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) afforded the aldehyde in 79% yield (1.02 g). TLC (silica, 10% $\text{MeOH}/\text{CH}_2\text{Cl}_2$): R_f = 0.67. MS (electrospray) calculated for $\text{C}_{21}\text{H}_{24}\text{F}_3\text{N}_3\text{O}_3$, 424.2 ($[\text{M}+\text{H}]^+$), m/z found, 424.2. ^1H NMR (400 MHz, CDCl_3): 9.82 (s, 1H), 7.65 (br d, J = 8.0 Hz, 2H), 7.54 (br s, 2H), 4.53 (s, 2H), 4.21 (t, J = 6.2 Hz, 2H), 3.68 (br s, 2H), 3.04 (t, J = 6.2 Hz, 2H), 2.70 (t, J = 5.6 Hz, 2H), 1.39 (s, 9H).

B. 1-{3-[4-(3-Methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester.

- 5 To a stirred solution of 1-(3-oxo-propyl)-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (0.99 g, 23.6 mmol) in CH₂Cl₂ (20 mL) were added 1-methyl-3-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (0.60 g, 25.9 mmol) and glacial AcOH (0.13 mL, 23.6 mmol) in that order and stirred for 20 min. NaBH(OAc)₃ (0.65 g, 30.6
- 10 mmol) was added and stirred under nitrogen for 2 h. Saturated NaHCO₃ (20 mL) was added and stirred for 30 min, and the layers were separated. The organic extract was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. MPLC of the crude afforded the desired compound as a white solid (1.27 g, 85%). TLC (silica, 7% MeOH/CH₂Cl₂): R_f = 0.35. MS
- 15 (electrospray): exact mass calculated for C₃₄H₄₁F₃N₆O₃, 638.32; *m/z* found, 639.3 [M+H]⁺, 661.2 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃): 7.81 (br d, *J* = 8.0 Hz, 2H), 7.68 (br s, 2H), 7.25 (dd, *J* = 1.6, 7.5 Hz, 1H), 7.15-7.07 (m, 2H), 7.02(dd, *J* = 1.6, 7.9 Hz, 1H), 4.70 (br s, 2H), 4.38 (tt, *J* = 4.2, 12.4 Hz, 1H), 4.18 (t, *J* = 6.8 Hz, 2H), 3.82 (s, 2H), 3.45 (s, 3H), 3.07 (d, *J* = 11.6 Hz, 2H),
- 20 2.84 (t, *J* = 5.5 Hz, 2H), 2.53-2.42 (m, 2H), 2.44 (t, *J* = 6.7 Hz, 2H), 2.21-2.03 (m, 4H), 1.84 (d, *J* = 12.0 Hz, 2H), 1.52 (s, 9H).

C. 1-Methyl-3-(1-{3-[3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one.

- 25 1-{3-[4-(3-Methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (1.19 g, 1.86 mmol) was dissolved in trifluoroacetic acid (5 mL) and CH₂Cl₂ (5 mL) and allowed to stir at room
- 30 temperature for 2 h. The reaction mixture was concentrated, diluted with CH₂Cl₂, and washed with saturated NaHCO₃. The organic layer was dried over Na₂SO₄ and concentrated to afford 1-methyl-3-(1-{3-[3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-

1,3-dihydro-benzoimidazol-2-one (0.955 g, 96%) as a white foam. TLC (silica, 10% MeOH/CH₂Cl₂): R_f = 0.19. MS (electrospray) calculated for C₂₉H₃₃F₃N₆O, 539.3 ([M+H]⁺), *m/z* found, 539.3.

5 D. 1-{3-[4-(3-Methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-sulfonic acid (*N*-*t*-butoxy carbonyl)amide.

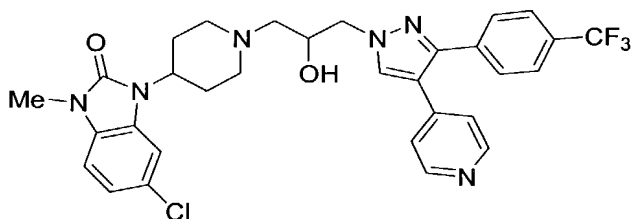
To a solution of chlorosulfonyl isocyanate (0.018 mL, 0.209 mmol) in CH₂Cl₂ (0.150 mL) was added 2-methyl-2-propanol (0.020 mL, 0.209 mmol) and the
10 solution was stirred at room temperature for 15 min. This solution was then added dropwise to a solution of 1-methyl-3-(1-{3-[3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one (75 mg, 0.139 mmol) and triethylamine (0.039 mL, 0.279 mmol) in CH₂Cl₂ (0.4 mL). An additional 0.15 mL of CH₂Cl₂ was
15 used to transfer all of the material to the reaction mixture. The reaction mixture was allowed to stir overnight. Column chromatography (silica, 2-10% MeOH/CH₂Cl₂) gave 93 mg (93%) of the title compound. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.24. MS (electrospray): calculated for C₃₄H₄₂F₃N₇O₅S, 718.3 ([M+H]⁺); *m/z* found, 718.3.

20 E. 1-{3-[4-(3-Methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-sulfonic acid amide.

1-{3-[4-(3-Methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-
25 3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-sulfonic acid (*N*-*t*-butoxy carbonyl)amide (75 mg, 0.105 mmol) was dissolved in trifluoroacetic acid (0.75 mL) and CH₂Cl₂ (0.75 mL). The reaction mixture was allowed to stir for 2 h, concentrated, diluted with CH₂Cl₂ (25 mL) and washed with saturated NaHCO₃. The organic layer was dried over Na₂SO₄,
30 concentrated, and purified by silica gel chromatography (5-10% MeOH/CH₂Cl₂) to afford 1-{3-[4-(3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-sulfonic acid amide (15 mg, 23%). MS (electrospray) calculated for

$C_{29}H_{34}F_3N_7O_3S$, 618.2 ($[M+H]^+$), m/z found, 618.2. 1H NMR (400 MHz, $CDCl_3$): 7.72 (d, $J = 8.2$ Hz, 2H), 7.63 (d, $J = 8.2$ Hz, 2H), 7.22 (br s, 1H), 7.04-7.11 (m, 2H), 6.95-7.00 (m, 1H), 5.02 (br s, 1H), 4.53 (s, 1H), 4.08-4.36 (m, 3H), 3.68 (br t, $J = 5.9$ Hz, 2H), 3.38 (s, 3H), 2.95-3.01 (m, 2H), 2.41-2.70 (m, 4H), 2.11-2.34 (m, 4H), 1.52-1.94 (m, 6H).

EXAMPLE 28



10 5-Chloro-3-(1-{2-hydroxy-3-[4-pyridin-4-yl-3-(4-trifluoromethyl-phenyl)-pyrazol-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-benzoimidazol-2-one.

A. 4-[1-Oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-pyridine.

15 To a solution of 4-[3-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-pyridine (0.5 g, 1.73 mmol) and epichlorohydrin (1.35 mL, 17.3 mmol) in DMF (2 mL) was added cesium carbonate (0.676 g, 2.07 mmol). The reaction mixture was allowed to stir for 24 h, diluted with EtOAc and washed successively with saturated $NaHCO_3$, water, and brine. The organic layer was dried over
20 Na_2SO_4 , concentrated and partially purified by running through a plug of silica gel (5% acetone/ CH_2Cl_2) to afford 4-[1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-pyridine (0.198 g, 33%) as an unstable oil. TLC (silica, 20% acetone/ CH_2Cl_2): $R_f = 0.39$. MS (electrospray): exact mass calculated for $C_{18}H_{14}F_3N_3O$, 346.1 $[M+H]^+$, m/z found, 346.1.

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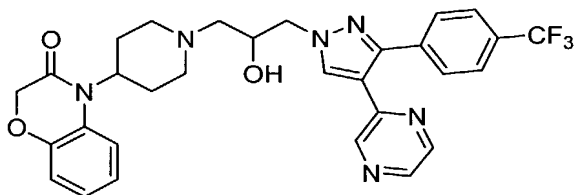
B. 5-Chloro-3-(1-{2-hydroxy-3-[4-pyridin-4-yl-3-(4-trifluoromethyl-phenyl)-pyrazol-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-benzoimidazol-2-one.

To a solution of 4-[1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-pyridine (68 mg, 0.197 mmol) and 5-chloro-1-methyl-3-piperidin-4-yl-1,3-

dihydro-benzoimidazol-2-one (0.055 g, 0.207 mmol) in EtOH (1 mL) was added triethylamine (0.027 mL, 0.197 mmol). The reaction mixture was heated at 80 °C overnight, concentrated, and purified by column chromatography (silica, 2-10% MeOH/CH₂Cl₂) to afford the title compound (0.026 g, 22%). MS

- 5 (electrospray): exact mass calculated for C₃₁H₃₀ClF₃N₆O₂, 611.2 [M+H]⁺, *m/z* found, 611.2. ¹H NMR (400 MHz, CDCl₃): 8.59 (br s, 2H), 8.20 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 5.9 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.35 (br s, 1H), 7.09 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 4.55-4.60 (m, 2H), 4.39 (d, *J* = 14.2, 4.1 Hz, 1H), 4.31 (d, *J* = 14.2, 6.1 Hz, 1H), 3.80-3.90 (m, 2H),
10 3.37 (s, 3H), 3.18-3.33 (m, 2H), 3.02-3.17 (m, 2H), 2.77-2.95 (m, 2H), 1.99 (t, *J* = 12.4 Hz, 2H).

EXAMPLE 29



- 15 4-(1-{2-Hydroxy-3-[4-pyrazin-2-yl-3-(4-trifluoromethyl-phenyl)-pyrazol-1-yl]-propyl}-piperidin-4-yl)-4H-benzo[1,4]oxazin-3-one.

- 20 A. 4-(2-Hydroxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester.
2-Aminophenol (15.0 g, 137 mmol) and 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (27.4 g, 138 mmol) were set stirring in CH₂Cl₂ (200 mL) at room temperature. Sodium triacetoxyborohydride (40.8 g, 193 mmol) was added in portions over 10 min followed by acetic acid (7.8 mL, 136 mmol). After 18 h
25 saturated NaHCO₃ was added, the organics separated, dried (MgSO₄) and evaporated to give 36.4 g (91%) of a beige solid. TLC (silica, 50% EtOAc/hexanes): R_f = 0.56. MS (electrospray): exact mass calculated for C₁₆H₂₄N₂O₃, 292.18; *m/z* found, 315.1 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃): 9.20 (s, 1H), 6.80-6.50 (m, 3H), 6.40 (t, *J* = 6.1 Hz, 1H), 4.30 (d, *J* = 8.7 Hz,

1H), 3.88 (d, $J = 12.6$ Hz, 2H), 3.45-3.35 (m, 1H), 3.00-2.75 (br s, 2H), 1.88 (d, $J = 10.5$ Hz, 2H), 1.40 (s, 9H), 1.30-1.20 (m, 2H).

B. 4-(2-Ethoxycarbonylmethoxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester.

A mixture of NaH (1.56 g, 65 mmol) in THF (100 mL) was set stirring and cooled to 5 °C. 4-(2-Hydroxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (17.5 g, 60 mmol) in THF (100 mL) was added dropwise over 30 min. After 2 h ethyl bromoacetate (7.3 mL, 66 mmol) was added. After stirring at room temperature for 24 h saturated NH_4Cl (100 mL) was added and the organics evaporated. The aqueous layer was extracted with EtOAc (2 x 150 mL). The organics were combined, dried (MgSO_4) and evaporated to give 24 g of a deep red liquid. The liquid was purified (silica, 5% acetone/ CH_2Cl_2) to give 21.4 g (94%) of a clear orange liquid. TLC (silica, 5% acetone/ CH_2Cl_2): $R_f =$ 0.48. MS (electrospray): exact mass calculated for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_5$, 378.22; m/z found, 379.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO): 7.02 (m, 1H), 6.90-6.70 (m, 3H), 4.74 (s, 2H), 4.37 (q, $J = 7.1$ Hz, 2H), 4.13 (br s, 2H), 3.60-3.50 (m, 1H), 3.08 (m, 2H), 2.16 (m, 2H), 1.60-1.50 (m, 2H), 1.58 (s, 9H), 1.41 (t, $J = 7.1$ Hz, 3H).

C. 4-(2-Carboxymethoxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester.

4-(2-Ethoxycarbonylmethoxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (21.4 g, 56.5 mmol) was set stirring in MeOH (150 mL). A solution of NaOH (4.5 g, 112.5 mmol) in water (150 mL) was added. After 3 h the mixture was acidified to pH 4 with 6 N HCl. MeOH was removed under reduced pressure and the aqueous layer extracted with EtOAc (2 x 150 mL). The organics were combined, dried (MgSO_4) and evaporated to give 20 g (100%) of a brown solid. MS (electrospray): exact mass calculated for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_5$, 350.18; m/z found, 351.2 $[\text{M}+\text{H}]^+$.

D. 4-(3-Oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-piperidine-1-carboxylic acid tert-butyl ester.

4-(2-Carboxymethoxy-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester (22 g, 63 mmol) was set stirring in CH₂Cl₂ (200 mL). EDC (13 g, 68 mmol) was added in one portion. After 30 min 1 N HCl was added. The organics were separated, dried (MgSO₄) and evaporated to give 17 g (81%) of a clear brown oil. TLC (silica, 5% acetone/CH₂Cl₂): R_f = 0.45. MS (electrospray): exact mass calculated for C₁₈H₂₄N₂O₄, 332.17; *m/z* found, 259.1 [M-BOC+H]⁺. ¹H NMR (400 MHz, CDCl₃): 7.30-7.20 (m, 1H), 7.15-7.10 (m, 3H), 4.61 (s, 2H), 4.60-4.45 (m, 1H), 4.45-4.30 (br s, 2H), 2.88 (t, *J* = 12.5 Hz, 2H), 2.65 (dd, *J* = 12.6, 4.5 Hz, 2H), 1.87 (d, *J* = 12.4 Hz, 2H), 1.60 (s, 9H).

E. 4-Piperidin-4-yl-4H-benzo[1,4]oxazin-3-one.

4-(3-Oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-piperidine-1-carboxylic acid tert-butyl ester (17 g, 51 mmol) and 1:1 TFA/ CH₂Cl₂ (40 mL) were combined and set stirring. After 45 min the mixture was evaporated to give a clear brown oil. The oil was set stirring and Et₂O was added (300 mL). A solid formed and was filtered, washed with Et₂O and air dried to give 16 g (90%) of a light beige solid. MS (electrospray): exact mass calculated for C₁₃H₁₆N₂O₂, 232.12; *m/z* found, 233.1 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD): 7.44 (dd, *J* = 6.5, 1.4 Hz, 1H), 7.20-7.7.10 (m, 3H), 4.58 (s, 2H), 4.55-4.45 (m, 1H), 4.65-4.55 (m, 2H), 3.27 (dt, *J* = 13.0, 2.3 Hz, 2H), 3.05 (dd, *J* = 12.3, 4.1 Hz, 2H), 2.15 (d, *J* = 13.8 Hz, 2H).

F. 2-[1-Oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-pyrazine.

To a solution of 2-[3-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-pyrazine (200 mg, 0.69 mmol) and epichlorohydrin (0.540 mL, 6.9 mmol) in DMF (2 mL) was added cesium carbonate (450 mg, 1.38 mmol). The reaction mixture was allowed to stir for 24 h, diluted with EtOAc, and washed with saturated NaHCO₃, water, and brine. The organic layer was dried over Na₂SO₄, concentrated and purified by column chromatography (silica, 5% acetone/CH₂Cl₂) to afford 2-[1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-pyrazine (141 mg, 59%). TLC (silica, 20% acetone/CH₂Cl₂): R_f =

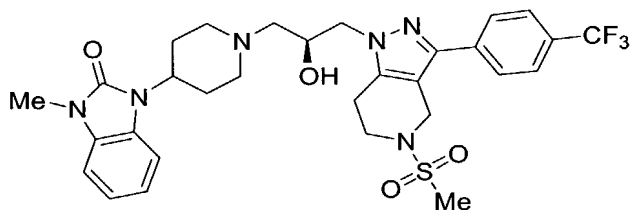
0.38. MS (electrospray) m/z 347.1 (347.1, calculated for $C_{17}H_{13}F_3N_4O$, $M^+ + H$).
 1H NMR (400 MHz, $CDCl_3$): 8.51 (dd, $J = 2.8, 1.8$ Hz, 1H), 8.45 (d, $J = 1.5$ Hz, 1H), 8.38 (d, $J = 12.8$ Hz, 1H), 8.01 (s, 1H), 7.66 (d, $J = 8.6$ Hz, 1H), 7.62 (d, $J = 8.6$ Hz, 1H), 4.57 (dd, $J = 14.7, 3.1$ Hz, 1H), 4.21 (dd, $J = 14.7, 6.1$ Hz, 1H),
 5 3.44 (m, 1H), 2.91 (t, $J = 4.5$ Hz, 1H), 2.62 (dd, $J = 4.0, 2.5$ Hz, 1H).

G. 4-(1-(2-Hydroxy-3-[4-pyrazin-2-yl-3-(4-trifluoromethyl-phenyl)-pyrazol-1-yl]-propyl)-piperidin-4-yl)-4H-benzo[1,4]oxazin-3-one.

To a solution of 2-[1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-pyrazine (76 mg, 0.220 mmol) and 4-piperidin-4-yl-4H-benzo[1,4]oxazin-3-one (61 mg, 0.231 mmol) in EtOH (1.1 mL) was added triethylamine (0.031 mL, 0.220 mmol). The reaction mixture was heated to 80 °C overnight, concentrated, and purified by column chromatography (silica, 5-10% MeOH/ CH_2Cl_2) to afford 4-(1-(2-hydroxy-3-[4-pyrazin-2-yl-3-(4-trifluoromethyl-phenyl)-pyrazol-1-yl]-propyl)-piperidin-4-yl)-4H-benzo[1,4]oxazin-3-one (27 mg, 21%). TLC (silica, 5% MeOH/ CH_2Cl_2): $R_f = 0.09$. MS (electrospray): m/z 579.2 (579.2, calculated for $C_{30}H_{29}F_3N_6O_3$, $M^+ + H$). 1H NMR (400 MHz, $CDCl_3$): 8.53 (s, 1H), 8.48 (s, 1H), 8.40 (s, 1H), 8.11 (s, 1H), 7.73 (d, $J = 8.2$ Hz, 2H), 7.63 (d, $J = 8.2$ Hz, 2H), 7.16 (d, $J = 5.4$ Hz, 1H), 7.00-7.03 (m, 3H), 4.49 (s, 2H),
 15 4.39 (d, $J = 10.8$ Hz, 1H), 3.13 (d, $J = 11.9$ Hz, 1H), 2.96 (d, $J = 11.9$ Hz, 1H), 2.59-2.80 (m, 2H), 2.40-2.55 (m, 3H), 2.17 (t, $J = 11.9$ Hz, 1H), 1.77 (d, $J = 11.9$ Hz, 2H).

EXAMPLE 30

25



(S)-1-(1-(2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl)-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one.

A. 4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester.

1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (7.24 g, 34.1 mmol) and di-
5 tert-butyl dicarbonate (9.12 g, 41.0 mmol) were combined in DMF (80 mL) and
the mixture heated to 40 °C under N₂ for 17 h. The mixture was allowed to
cool, diluted with EtOAc (800 mL) and washed with saturated NaHCO₃ (150
mL), H₂O (3 x 150 mL) and brine (150 mL). The combined aqueous washes
were extracted with EtOAc (2 x 150 mL). The combined extracts were dried
10 over Na₂SO₄ and concentrated, to give 4-(2-oxo-2,3-dihydro-benzoimidazol-1-
yl)-piperidine-1-carboxylic acid tert-butyl ester (12.36 g, 94%). TLC (silica, 50%
EtOAc/hexanes): R_f = 0.3. MS (electrospray): exact mass calculated for
C₁₇H₂₃N₃O₃, 340.16; m/z found, 340.1 [M + Na]⁺. ¹H NMR (CDCl₃, 400 MHz):
10.59 (s, 1H), 7.15-7.11 (m, 2H), 7.08-7.02 (m, 2H), 4.49 (tt, J = 8.4, 4.0 Hz,
15 1H), 4.32 (br s, 2H), 2.89 (br t, J = 11.6, 2H), 2.34 (dq, J = 12.6, 4.4 Hz, 2H),
1.83 (br d, J = 10.5 Hz, 2H) 1.36 (s, 9H).

B. 1-Methyl-3-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one.

A solution of KHMDS (5.07 g, 25.4 mmol) in THF (40 mL plus a 10 mL rinse)
20 was added via cannula to a solution of 4-(2-oxo-2,3-dihydro-benzoimidazol-1-
yl)-piperidine-1-carboxylic acid tert-butyl ester (6.64 g, 20.2 mmol) in THF (20
mL). The mixture was stirred for 25 min then iodomethane (5.2 mL, 84 mmol)
was added. The resulting mixture was stirred for 45 min then diluted with
EtOAc (700 mL). The EtOAc was washed with H₂O (3 x 200 mL), saturated
25 NaHCO₃ (150 mL) and brine (150 mL). The combined washes were extracted
with EtOAc (2 x 150 mL). The combined extracts were dried over Na₂SO₄ and
concentrated. The crude reaction mixture was purified by column
chromatography (silica, 15-60% EtOAc/hexanes) to give the methylated adduct
(5.21 g, 78%). The purified material was dissolved in a mixture of CH₂Cl₂ (40
30 mL) and TFA (35 mL). The mixture was stirred for 4 h then concentrated in
vacuo. The residue was dissolved in CH₂Cl₂ (300 mL) and washed with
saturated NaHCO₃ (100 mL). The aqueous layer was extracted with
5%MeOH/CH₂Cl₂ (4 x 150 mL). The combined extracted were dried over

Na₂SO₄ and concentrated to yield the title compound (3.85 g, containing inorganic salts) which was suitable for further use. TLC (silica, 5% MeOH/CH₂Cl₂): R_f = 0.1. MS (electrospray): exact mass calculated for C₁₃H₁₈N₃O, 232.14; *m/z* found 232.1 [M + H]⁺. ¹H NMR (CDCl₃, 400 Hz): 7.27-7.29 (m, 1H), 7.05-7.12 (m, 2H), 6.99 (dd, *J* = 6.1, 2.1 Hz, 1H), 4.45 (tt, *J* = 12.5, 4.2 Hz, 1H), 3.42 (s, 3H), 3.27 (dd, *J* = 10.2, 2.1 Hz, 2H), 2.81 (dt, *J* = 2.4, 12.4 Hz, 2H), 2.35 (dq, *J* = 12.5, 4.2 Hz, 2H), 2.26 (br s, 1H), 1.83 (dd, *J* = 12.1, 2.1 Hz, 2H).

10 C. (*R*)-tert-Butyl-dimethyl-oxiranylmethoxy-silane.

tert-Butyl-chloro-dimethylsilane (12.9 g, 85.5 mmol) followed by Et₃N (19 mL, 136 mmol) was added to a 0 °C solution of (*S*)-(+)-glycidol (5.0 g, 67 mmol) in CH₂Cl₂ (200 mL). The solution was allowed to warm to 23 °C with stirring over 17 h. The resulting pink solution was diluted with Et₂O (800 mL) and stirred an additional 30 min. The Et₂O layer was washed with saturated aqueous NaHCO₃ (200 mL), H₂O (2 x 100 mL), brine (100 mL), dried over Na₂SO₄ and concentrated. Purification by column chromatography (silica, 5-10% Et₂O/hexanes) gave (*R*)-tert-Butyl-dimethyl-oxiranylmethoxy-silane (10.01 g, 79%). TLC (silica, 10% Et₂O/hexanes): R_f = 0.5. ¹H NMR (CDCl₃, 400 MHz): 3.85 (dd, *J* = 11.9, 3.2 Hz, 1H), 3.66 (dd, *J* = 11.9, 4.8 Hz, 1H), 3.09 (m, 1H), 2.77 (dd, *J* = 5.0, 4.2 Hz, 1H), 2.64 (dd, *J* = 5.2, 2.7 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

25 D. (*R*)-3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-*c*]pyridin-1-yl]-propane-1,2-diol.

Cs₂CO₃ (1.88 g, 5.77 mmol) was added to a solution of (*R*)-tert-Butyl-dimethyl-oxiranylmethoxy-silane (2.72 g, 14.4 mmol) and 5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-*c*]pyridine (1.70g, 4.81 mmol) in DMF (13 mL). The mixture was stirred at room temperature for 5 days, then partitioned between EtOAc (400 mL) and saturated NaHCO₃ (100 mL). The EtOAc layer was washed with H₂O (3 x 75 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated. The residue was dissolved in MeOH (125 mL) and treated with CSA (800 mg). The mixture was stirred for 20 h

then concentrated. The residue was re-dissolved in EtOAc (200 mL), washed with saturated NaHCO_3 (100 mL), dried over Na_2SO_4 and concentrated.

Purification by column chromatography (silica, 20-60% acetone/ CH_2Cl_2) gave the corresponding diol (0.78 g, 40%). TLC (25% acetone/ CH_2Cl_2): $R_f = 0.2$. MS (electrospray): exact mass calculated for $\text{C}_{17}\text{H}_{21}\text{F}_3\text{N}_3\text{O}_4\text{S}$, 420.11; m/z found, 420.1 $[\text{M} + \text{H}]^+$. ^1H NMR ($\text{CD}_3\text{OD}/\text{CDCl}_3$, 400 MHz): 7.74 and 7.67 (A and B of AA'BB', $J_{ab} = 8.3$ Hz, 4H), 4.52 (s, 2H), 4.23 (dd, $J = 13.0, 3.0$ Hz, 1H), 4.04-4.11 (m, 2H), 3.64 (t, $J = 5.9$ Hz, 2H), 3.52 and 3.57 (A and B of ABX, $J_{ab} = 11.4$, $J_{ax} = 4.8$, $J_{bx} = 4.9$ Hz, 2H), 2.98 (m, 2H), 2.91 (s, 3H).

E. (R)-5-Methanesulfonyl-1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine.

PpTs (271 mg, 1.1 mmol) and (R)-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propane-1,2-diol (317 mg, 0.756 mmol) were combined in trimethylorthoacetate (30 mL). The mixture was stirred for 18 h then diluted with EtOAc (125 mL), washed with saturated NaHCO_3 (2 x 50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated. Purification by chromatography (silica, 100%EtOAc) gave the corresponding orthoacetate (313 mg, 0.678 mmol). The purified orthoacetate was dissolved in CH_2Cl_2 (2.25 mL), cooled to 0 °C, and treated with MeOH (25 μL) and AcBr (110 μL , 1.48 mmol). The mixture was allowed to warm over 3 h, then partitioned between EtOAc (50 mL) and saturated NaHCO_3 (20 mL). The EtOAc layer was washed with saturated NaHCO_3 (2 x 20 mL). The combined washes were extracted with EtOAc (3 x 20 mL). The combined extracts were dried over Na_2SO_4 and concentrated. The residue was dissolved in EtOH (40 mL) and treated with KOEt (1.0 mL, 40 wt% solution in EtOH). After 1 h the mixture was concentrated to ca. 20 mL and worked up as above. Purification by column chromatography (silica, 100% EtOAc) gave the epoxide (189 mg, 62%). TLC (100% EtOAc): $R_f = 0.35$. MS (electrospray): exact mass calculated for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_3\text{O}_3\text{S}$, 402.10; m/z found, 402.1 $[\text{M} + \text{H}]^+$. ^1H NMR (CDCl_3 , 400 MHz): 7.72 and 7.67 (A and B of AA'BB', $J_{ab} = 8.3$ Hz, 4H), 4.57 and 4.53 (A and B of AB, $J_{ab} = 12.9$ Hz, 2H), 4.52 (dd, $J = 15.2, 2.7$ Hz, 1H),

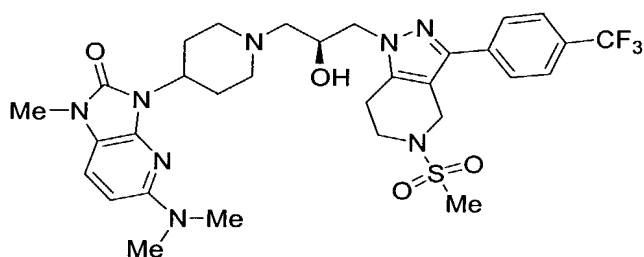
4.12 (dd, $J = 15.2, 5.4$ Hz, 1H), 3.67 (m, 2H), 3.36 (m, 1H), 2.92 (m, 2H), 2.88 (s, 3H), 2.85 (dd, $J = 4.4, 4.3$ Hz, 1H), 2.49 (dd, $J = 4.6, 2.6$ Hz, 1H).

F. (S)-1-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-

5 4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one.

A solution of (*R*)-5-methanesulfonyl-1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (134 mg, 0.334 mmol) and 1-methyl-3-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (110 mg, 0.476 mmol) in EtOH (0.8 mL) and dichloroethane (0.8 mL) was heated to 80 °C for 18 h. The mixture was then concentrated and the residue purified by column chromatography (silica, 0-50% acetone/CH₂Cl₂) to give the title compound (134 mg, 86%). TLC (20% acetone/CH₂Cl₂) $R_f = 0.3$. MS (electrospray): calculated for C₃₀H₃₆F₃N₆O₄S, [M + H]⁺ 633.24; m/z found, 633.3. ¹H NMR (CDCl₃, 400 MHz): 7.72 and 7.66 (A and B of AA'BB', $J_{ab} = 8.3$ Hz, 4H), 7.15 (dd, $J = 7.0, 1.7$ Hz, 1H), 7.08 (m, 2H), 6.98 (dd, $J = 6.6, 1.8$ Hz, 1H), 4.60 and 4.55 (A and B of AB, $J_{ab} = 14.5$ Hz, 2H), 4.34 (m, 1H), 4.23 (dd, $J = 13.8, 2.8$ Hz, 1H), 4.15 (m, 1H), 4.23 (dd, $J = 13.8, 6.6$ Hz, 1H), 3.71 (m, 2H), 3.40 (s, 3H), 3.08 (m, 2H), 2.96 (m, 2H), 2.89 (s, 3H), 2.56-2.36 (m, 4H), 2.23 (d, $J = 11.6$ Hz, 1H), 20 1.81 (m, 2H).

EXAMPLE 31



25 (S)-5-Dimethylamino-3-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one.

A. 4-(6-Chloro-3-nitro-pyridin-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester.

A stirring solution of 20 g (0.10 mol) of 2,6-dichloro-3-nitro-pyridine in DMF (245 mL) was cooled to 0 °C. After 5 min, 9.87 g (0.05 mol) of 4-amino-piperidine-1-carboxylic acid tert-butyl ester and 6.8 g (0.05 mol) of K₂CO₃ were added, resulting in a suspension. The mixture was allowed to stir for 5 h at 0 °C. The mixture was then partitioned between water (300 mL) and EtOAc (400 mL). The aqueous layer was then extracted with EtOAc (5 x 400 mL). The organic layer was dried over anhydrous Na₂SO₄, and concentrated to give a brown oil. The product was purified using silica gel chromatography (silica, 100%CH₂Cl₂, then 10% EtOAc/hexanes) to afford 8.99 g (51%) of the desired product as a bright yellow solid. MS (electrospray): exact mass calculated for C₁₅H₂₁ClN₄O₄, 356.13; *m/z* found, 379.1 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃): 8.36 (d, *J* = 8.4 Hz, 1H), 8.27 (d, *J* = 7.3 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.38-4.26 (m, 1H), 4.14-3.96 (m, 2H), 3.01 (t, *J* = 11.6 Hz, 2H), 2.05 (dd, *J* = 12.4 Hz, 3.03 Hz, 2H), 1.58-1.44 (m, 2H), 1.47 (s, 9H).

B. 4-(6-Dimethylamino-3-nitro-pyridin-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester.

To a stirring solution of 6 g (0.016 mol) of 4-(6-chloro-3-nitro-pyridin-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester in MeOH/CH₂Cl₂ (84 mL/15 mL) was added 2.2 g (0.05 mol) of dimethylamine in THF (25 mL). The reaction mixture was stirred at room temperature for 16 h, and was then concentrated. The crude product was then dissolved in CH₂Cl₂ (400 mL) and washed with saturated NaHCO₃ (2 x 200 mL). The washes were combined and extracted with EtOAc (100 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to afford 6.1 g (99%) of the desired product as a bright yellow solid. MS (electrospray): exact mass calculated for C₁₇H₂₇N₅O₄, 365.21; *m/z* found, 388.19 [M+Na]⁺. ¹H NMR (400 MHz, CDCl₃): 8.74 (d, *J* = 7.07 Hz, 1H), 8.18 (d, *J* = 9.4 Hz, 1H), 5.97 (d, *J* = 7.3 Hz, 1H), 4.28-4.16 (m, 1H), 4.07-3.93 (m, 2H), 3.17 (s, 6H), 3.01 (t, *J* = 11.9 Hz, 2H), 2.05 (dd, *J* = 12.4 Hz and 3.03 Hz, 2H), 1.60-1.50 (m, 2H), 1.47 (s, 9H).

C. 4-(5-Dimethylamino-1-methyl-2-oxo-1,2-dihydro-imidazo[4,5-b]pyridin-3-yl)-piperidine-1-carboxylic acid tert-butyl ester.

A stirring solution of 5.3 g (0.014 mol) of 4-(6-dimethylamino-3-nitro-pyridin-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester in methanol/EtOAc (73 mL/15 mL) was degassed. 10% Pd/C (1.17 g, 0.5 mmol) was added as a suspension in EtOH (5 mL), followed by ammonium formate (4.5 g, 0.073 mol). The mixture was stirred at room temperature for 3 h. The reaction mixture was then filtered through celite and the filtrate was concentrated, giving a purple oil. The residue was then dissolved in THF (73 mL), and 11.7 g (0.073 mol) of CDI was added, and the reaction was heated to 98 °C and stirred for 16 h. The mixture was then cooled and concentrated. The crude product was then partitioned between EtOAc (800 mL) and NaHCO₃ (100 mL), and the organic layer was washed with water (5 x 100 mL) and NaCl (100 mL). The combined aqueous layers were back-extracted with EtOAc (150 mL). The resulting organic layers were combined and dried over Na₂SO₄ and concentrated. The residue (2.4 g) was dissolved in THF (73 mL). To this stirring solution was added KHMDS (3.46 g, 0.017 mol) and iodomethane (10.3 g, 0.072 mol), and the mixture was allowed to stir for 20 min. The solvent was then concentrated, and the crude product was partitioned between EtOAc (600 mL) and NaHCO₃ (200 mL). The organic layer was washed with NaHCO₃ (150 mL), dried over Na₂SO₄, and concentrated. Purification using flash chromatography (silica, 80% EtOAc/hexanes) afforded 2.4 g (67% yield, 3 steps, based upon using 2/3 material at methylation stage) of desired product as a white solid. MS (electrospray): exact mass calculated for C₁₉H₂₉N₅O₃, 375.23; *m/z* found, 276.17 [M+H-100]⁺. ¹H NMR: (400MHz, CDCl₃): 7.02 (d, *J* = 8.6 Hz, 1H), 6.15 (d, *J* = 8.6 Hz, 1H), 4.46 (tt, *J* = 12.0 Hz and 4.0 Hz, 1H), 4.38-4.11(m, 2H), 3.33 (s, 3H), 3.01 (s, 6H), 2.95-2.73 (m, 2H), 2.73-2.55 (m, 2H), 1.77-1.61 (m, 2H), 1.47 (s, 9H).

30 D. 5-Dimethylamino-1-methyl-3-piperidin-4-yl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one.

To a stirring solution of 1.07 g (0.0028 mol) of 4-(5-dimethylamino-1-methyl-2-oxo-1,2-dihydro-imidazo[4,5-b]pyridin-3-yl)-piperidine-1-carboxylic acid tert-

butyl ester in CH_2Cl_2 (7 mL) was added 7 mL of TFA. After 35 min, the solvent was removed. The residue was partitioned between EtOAc (200 mL) and 1 N NaOH (150 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated to afford 0.74 g (96%) of 5-dimethylamino-1-methyl-3-piperidin-4-yl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one as a white/pink solid. ^1H NMR (400MHz, CDCl_3): 6.95 (d, $J = 8.3$ Hz, 1H), 6.08 (d, $J = 8.3$ Hz, 1H), 4.35 (tt, $J = 12.1$ Hz, 4.0 Hz, 1H), 3.25 (s, 3H), 3.14 (d, $J = 12.4$ Hz, 2H) 2.97 (s, 6H), 2.66 (td, $J = 12.9$ Hz, 1.3 Hz, 2H), 2.53 (qd, $J = 12.4$ Hz, 4.0 Hz, 2H), 1.69 (d, $J = 11.9$ Hz, 2H).

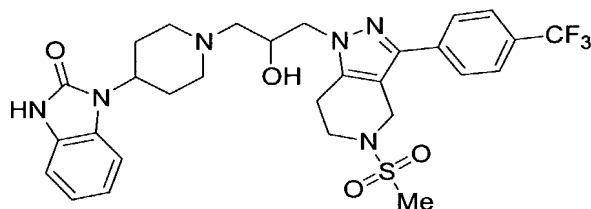
10

E. (S)-5-Dimethylamino-3-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one.

To a stirring solution of 0.24 g (0.0009 mol) of 5-dimethylamino-1-methyl-3-piperidin-4-yl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one in EtOH/Dichloroethane (1.5 mL/1.5 mL) was added 0.23 g (0.0005 mol) of (*R*)-5-methanesulfonyl-1-oxiranylmethyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine. The reaction mixture was heated to 80 °C and stirred for 16 h and concentrated. The crude product was then dissolved in CH_2Cl_2 (40 mL) and purified using flash chromatography (0-6% MeOH/ CH_2Cl_2) affording 0.38 g (97%) of the desired product as a white solid. MS (electrospray): exact mass calculated for $\text{C}_{31}\text{H}_{39}\text{F}_3\text{N}_8\text{O}_4\text{S}$, 676.28; m/z found, 677.28 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): 7.71 and 7.67 (A and B of AA'BB' quartet, $J_{ab} = 8.3$ Hz, 4H), 7.03 (d, $J = 8.6$ Hz, 1H), 6.16 (d, $J = 8.6$ Hz, 1H), 4.58 and 4.56 (A and B of AB quartet, $J_{ab} = 14.5$ Hz, 2H), 4.36 (tt, $J = 12.1$ Hz, 4.04 Hz, 1H), 4.25-4.01 (m, 4H), 3.77-3.60 (m, 2H), 3.33 (s, 3H), 3.16-3.04 (m, 2H), 3.03 (s, 6H), 2.99-2.90 (m, 2H), 2.88 (s, 3H), 2.77 (qd, $J = 12.1$ Hz, 3.54 Hz, 2H), 2.56-2.42 (m, 3H), 2.21 (t, $J = 11.6$ Hz, 1H), 1.75 (d, $J = 11.6$ Hz, 2H).

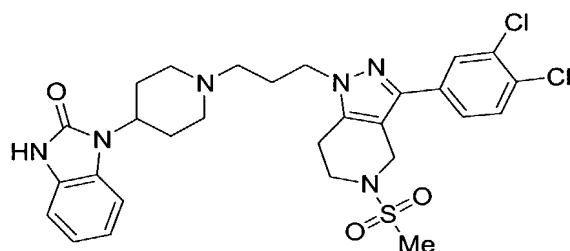
T09T09" 42C 23560

EXAMPLE 32



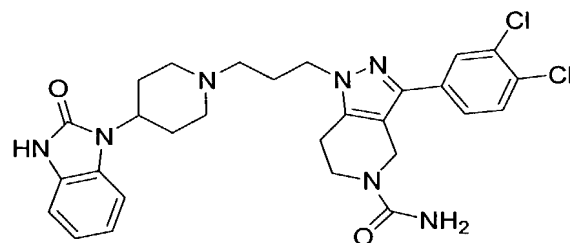
1-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-
 5 tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-
 benzoimidazol-2-one.

EXAMPLE 33



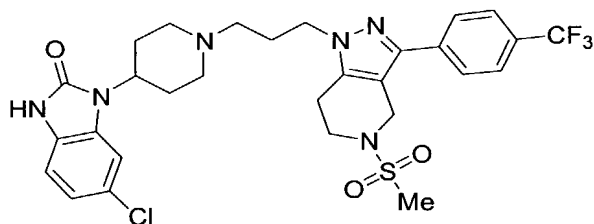
10 1-(1-{3-[3-(3,4-Dichloro-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-
 pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-
 one.

15 EXAMPLE 34



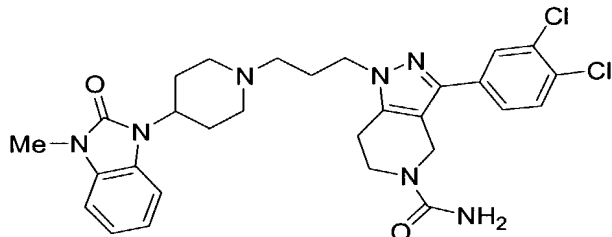
20 3-(3,4-Dichloro-phenyl)-1-{3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-
 piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic
 acid amide.

EXAMPLE 35



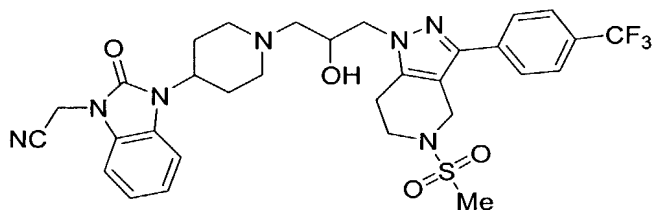
6-Chloro-1-(1-{3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one.

EXAMPLE 36



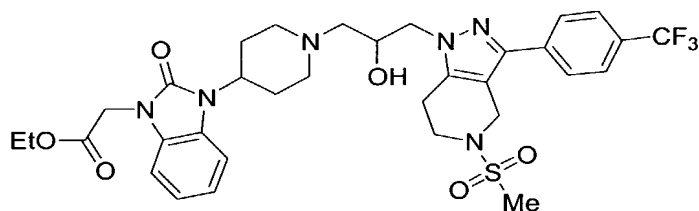
3-(3,4-Dichloro-phenyl)-1-{3-[4-(3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide.

EXAMPLE 37



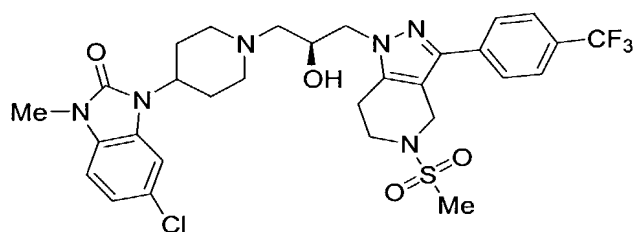
[3-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-acetonitrile.

EXAMPLE 38



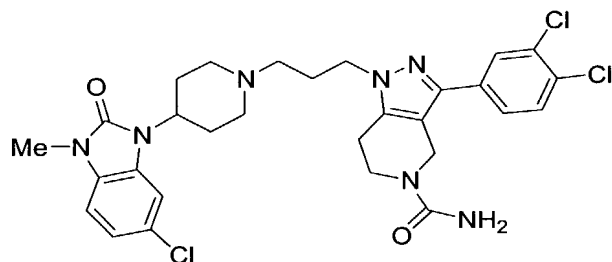
5 [3-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-acetic acid ethyl ester.

EXAMPLE 39



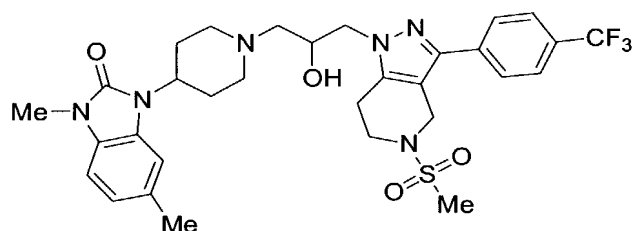
10 5-Chloro-3-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-benzoimidazol-2-one.

15 EXAMPLE 40



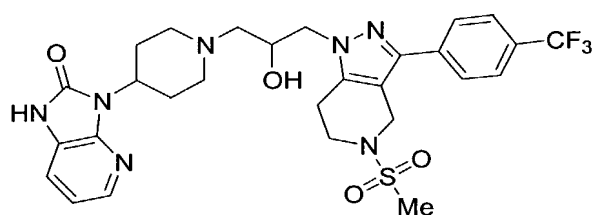
20 1-{3-[4-(6-Chloro-3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(3,4-dichloro-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide.

EXAMPLE 41



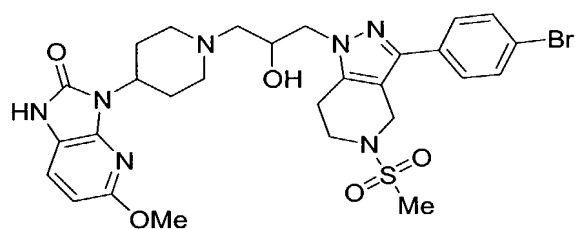
3-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,5-dimethyl-1,3-dihydro-benzoimidazol-2-one.

EXAMPLE 42



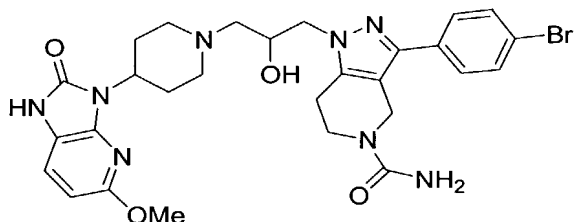
3-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one.

EXAMPLE 43



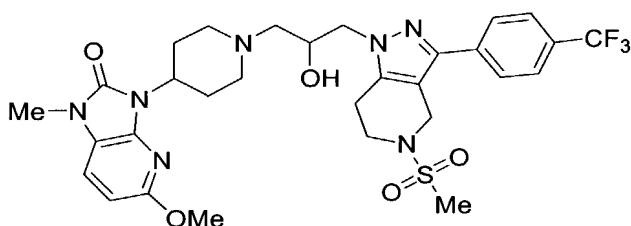
3-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-methoxy-1,3-dihydro-imidazo[4,5-b]pyridin-2-one.

EXAMPLE 44



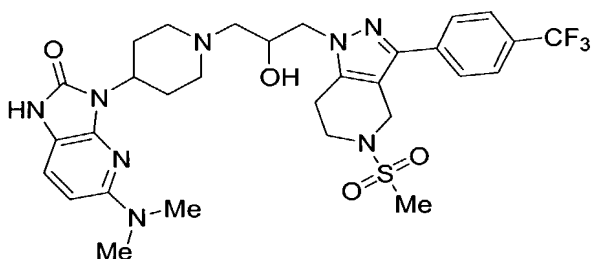
- 3-(4-Bromo-phenyl)-1-{2-hydroxy-3-[4-(5-methoxy-2-oxo-1,2-dihydro-imidazo[4,5-b]pyridin-3-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide.

EXAMPLE 45



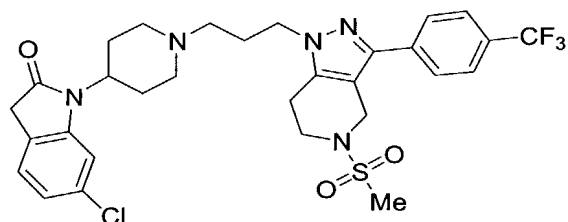
- 3-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-methoxy-1-methyl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one.

EXAMPLE 46



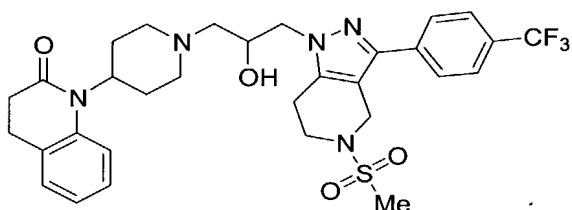
- 5-Dimethylamino-3-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one.

EXAMPLE 47



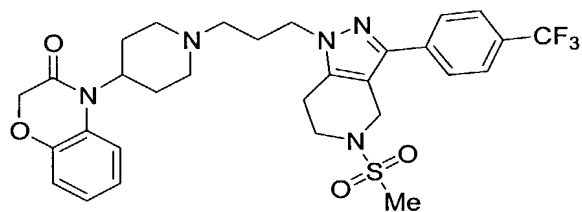
6-Chloro-1-(1-{3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one.

EXAMPLE 48



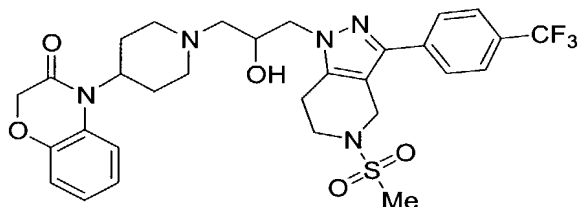
1-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one.

EXAMPLE 49



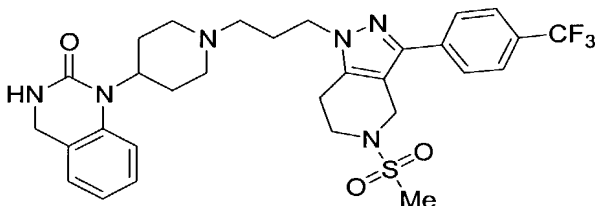
4-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-benzo[1,4]oxazin-3-one.

EXAMPLE 50



4-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-benzo[1,4]oxazin-3-one.

EXAMPLE 51



1-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinazolin-2-one.

EXAMPLE 52

15

Cathepsin S Inhibition Assay.

Recombinant human cathepsin S (CatS) was expressed in the baculovirus system and purified in one step with a thiopropyl-sepharose column. 10-L yielded ~700 mg of CatS and N-terminal sequencing confirmed identity. The assay is run in 100 mM sodium acetate pH 5.0 containing 1 mM DTT and 100 mM NaCl. The substrate for the assay is

(Aedens)EKARVLAEAA(Dabcyl)K-amide

25

- The K_m for the substrate is around 5 μM but the presence of substrate inhibition makes kinetic analysis difficult. With 20 μM substrate the assay rate is linear over the range of 1-8 ng CatS in 100 μl reaction. Using 2 ng/well of CatS, the production of product is linear and yields ~7-fold signal after 20 min with only
- 5 20% loss of substrate. Primary assays are run by quenching the reaction after 20 min with 0.1% SDS and then measuring the fluorescence. For other assays, measurements are taken every min for 20 min. The rate is calculated from the slope of the increase and the percent inhibition is calculated from this (See Tables 1, 2 and 3 below).

10

09927324-084004

Table 1

EXAMPLE	IC ₅₀ (μM)
1	0.73
2	0.07
3	0.28
4	0.19
5	1.16
6	0.19
7	0.26
8	0.04
9	0.10
10	0.09
11	0.03
12	0.62
13	0.37
14	0.29
15	0.23
16	0.30
17	1.30
18	0.25
19	0.02
20	0.01
21	0.02
22	0.03
23	0.08
24	0.03
25	0.23
26	0.18
27	0.09
28	0.89

EXAMPLE (Table 1, cont'd)	IC ₅₀ (μM) (Table 1, cont'd)
29	0.78
30	0.04
31	0.07

Table 2

EXAMPLE	IC ₅₀ (μM)
32	0.06
33	0.01
34	0.02
35	0.03
36	0.04
37	0.05
38	0.02
39	0.04
40	0.04
41	0.03
42	0.08
43	0.02
44	0.03
45	0.02
46	0.03
47	0.04
48	0.02
49	0.02
50	0.02
51	0.02

EXAMPLE 101

1-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-
pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-octahydro-benzoimidazol-2-
5 one

EXAMPLE 102

1-(1-{3-[5-Acetyl-3-(3,4-dichloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-
c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-octahydro-benzoimidazol-2-one
10

EXAMPLE 103

Acetic acid 1-(1-{3-[5-acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-
pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1H-benzoimidazol-2-yl ester

15 EXAMPLE 104

Methanesulfonic acid 1-(1-{3-[3-(4-bromo-phenyl)-5-methanesulfonyl-4,5,6,7-
tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1H-benzoimidazol-
2-yl ester

20 EXAMPLE 105

1-(1-{3-[5-Acetyl-3-(3,4-dichloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-
c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-chloro-1,3-dihydro-indol-2-one

EXAMPLE 106

25 1-{3-[4-(5-Chloro-2-oxo-2,3-dihydro-indol-1-yl)-piperidin-1-yl]-propyl}-3-(3,4-
dichloro-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid
amide

EXAMPLE 107

30 1-{3-[4-(5-Chloro-2-oxo-2,3-dihydro-indol-1-yl)-piperidin-1-yl]-propyl}-3-(3,4-
dichloro-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid
methanamide

EXAMPLE 108

Acetic acid 1-(1-{3-[5-acetyl-3-(3,4-dichloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1H-benzoimidazol-2-yl ester

5 EXAMPLE 109

Methanesulfonic acid 1-(1-{3-[3-(3,4-dichloro-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1H-benzoimidazol-2-yl ester

10 EXAMPLE 110

1-[1-{3-[4-(3,5-Dichloro-pyridin-4-ylamino)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

15 EXAMPLE 111

1-[1-{3-[4-(Benzooxazol-2-yloxy)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 112

20 1-[1-{3-[4-(Benzooxazol-2-ylamino)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 113

25 1-(4-Benzooxazol-2-yl-piperidin-1-yl)-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propan-2-ol

EXAMPLE 114

1-(4-Benzothiazol-2-yl-piperidin-1-yl)-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propan-2-ol

30

EXAMPLE 115

1-{3-[4-(5-Methyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide

5

EXAMPLE 116

N-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-N-(3-chloro-phenyl)-benzamide

10 EXAMPLE 117

4-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-methyl-4H-benzo[1,4]oxazin-3-one

EXAMPLE 118

15 4-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-methyl-4H-benzo[1,4]oxazin-3-one

EXAMPLE 119

20 3-(4-Bromo-phenyl)-1-{3-[4-(5-methyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide

EXAMPLE 120

25 4-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-methyl-4H-benzo[1,4]oxazin-3-one

EXAMPLE 121

30 4-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-methyl-4H-benzo[1,4]oxazin-3-one

EXAMPLE 122

3-(4-Bromo-phenyl)-1-{3-[4-(6-ethanesulfonyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide

5

EXAMPLE 123

4-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-6-ethanesulfonyl-4H-benzo[1,4]oxazin-3-one

10 EXAMPLE 124

4-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-6-ethanesulfonyl-4H-benzo[1,4]oxazin-3-one

15 EXAMPLE 125

1-[1-[3-(4-Benzothiazol-2-yl-piperidin-1-yl)-2-hydroxy-propyl]-3-(4-chloro-3-methyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 126

20 1-[1-[3-(4-Benzothiazol-2-yl-piperidin-1-yl)-2-hydroxy-propyl]-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 127

25 1-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-3,4-dihydro-1H-quinolin-2-one

EXAMPLE 128

30 1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-3,4-dihydro-1H-quinolin-2-one

EXAMPLE 129

1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-3,4-dihydro-1H-quinolin-2-one

5 EXAMPLE 130

1-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-3,4-dihydro-1H-quinazolin-2-one

10 EXAMPLE 131

1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-3,4-dihydro-1H-quinazolin-2-one

15 EXAMPLE 132

1-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-3-[4-(6-chloro-2,2-dioxo-3,4-dihydro-2H-2λ⁶-2,1,3-benzothiadiazin-1-yl)-piperidin-1-yl]-propan-2-ol

20 EXAMPLE 133

1-[4-(6-Chloro-2,2-dioxo-2,3-dihydro-2λ⁶-2,1,3-benzothiadiazol-1-yl)-piperidin-1-yl]-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propan-2-ol

25 EXAMPLE 134

1-[1-{3-[4-(6-Chloro-2,2-dioxo-2,3-dihydro-2λ⁶-2,1,3-benzothiadiazol-1-yl)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

30 EXAMPLE 135

4-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-4-1,4-benzoxazin-3-one

EXAMPLE 136

1-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one

5 EXAMPLE 137

1-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one

EXAMPLE 138

10 4-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-4H-1,4-benzoxazin-3-one

EXAMPLE 139

15 4-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-4H-1,4-benzoxazin-3-one

EXAMPLE 140

20 1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one

EXAMPLE 141

25 1-{2-Hydroxy-3-[4-(2-oxo-3,4-dihydro-2H-quinolin-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

EXAMPLE 142

30 1-{2-Hydroxy-3-[4-(3-oxo-2,3-dihydro-1,4-benzoxazin-4-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

EXAMPLE 143

4-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-4H-1,4-benzoxazin-3-one

5

EXAMPLE 144

4-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-1,4-benzoxazin-3-one

10 EXAMPLE 145

1-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one

EXAMPLE 146

15 1-{3-[4-(2-Oxo-3,4-dihydro-2H-quinolin-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

EXAMPLE 147

20 1-{3-[4-(3-Oxo-2,3-dihydro-1,4-benzoxazin-4-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

EXAMPLE 148

25 6-Chloro-4-(1-{3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-1,4-benzoxazin-3-one

EXAMPLE 149

30 4-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-6-chloro-4H-1,4-benzoxazin-3-one

090734-031001

EXAMPLE 150

4-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-1,4-benzoxazin-3-one

5 EXAMPLE 151

1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one

EXAMPLE 152

10 4-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-4H-1,4-benzoxazin-3-one

EXAMPLE 153

15 1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one

EXAMPLE 154

20 1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one

EXAMPLE 155

1-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one

25 EXAMPLE 156

1-(1-{3-[5-Acetyl-3-(3-chloro-4-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one

EXAMPLE 157

30 1-(1-{3-[3-(4-Chloro-3-methyl-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one

090724-081001

EXAMPLE 158

1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one

5 EXAMPLE 159

1-(1-{3-[5-Acetyl-3-(4-nitro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one

EXAMPLE 160

10 1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one

EXAMPLE 161

15 1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-1,3-dihydro-indol-2-one

EXAMPLE 162

20 6-Chloro-1-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one

EXAMPLE 163

25 1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-chloro-1,3-dihydro-indol-2-one

EXAMPLE 164

30 5-Chloro-1-(1-{3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one

EXAMPLE 165

1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-chloro-1,3-dihydro-indol-2-one

EXAMPLE 166

1-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-chloro-1,3-dihydro-indol-2-one

5

EXAMPLE 167

4-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-4*H*-pyrido[3,2-*b*]-1,4-oxazin-3-one

10

EXAMPLE 168

1-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,5-dihydro-4,1-benzoxazepin-2-one

15

EXAMPLE 169

1-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,4-dihydro-3,1-benzoxazin-2-one

20

EXAMPLE 170

1-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,4-dihydro-3,1-benzoxazin-2-one

25

EXAMPLE 171

1-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,5-dihydro-4,1-benzoxazepin-2-one

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EXAMPLE 172

1-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,4-dihydro-3,1-benzoxazin-2-one

5

EXAMPLE 173

1-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,4-dihydro-3,1-benzoxazin-2-one

10

EXAMPLE 174

1-(3-(4-Chloro-3-methyl-phenyl)-1-{2-hydroxy-3-[4-(5-nitro-2,3-dihydro-indol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

15

EXAMPLE 175

1-(3-(4-Chloro-3-methyl-phenyl)-1-{2-hydroxy-3-[4-(6-nitro-2,3-dihydro-indol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

20

EXAMPLE 176

1-(3-(4-Chloro-3-methyl-phenyl)-1-{2-hydroxy-3-[4-(2-methyl-2,3-dihydro-indol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

25

EXAMPLE 177

1-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinazolin-2-one

30

EXAMPLE 178

1-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinazolin-2-one

EXAMPLE 179

1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinazolin-2-one

5

EXAMPLE 180

1-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinazolin-2-one

10 EXAMPLE 181

1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinazolin-2-one

EXAMPLE 182

15 1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1-(3-chloro-phenyl)-3-methyl-urea

EXAMPLE 183

20 1-[3-(4-Benzotriazol-1-yl-piperidin-1-yl)-2-hydroxy-propyl]-3-(3,4-dichloro-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

EXAMPLE 184

25 1-{3-[4-(5-Chloro-2-oxo-2,3-dihydro-indol-1-yl)-piperidin-1-yl]-propyl}-3-(3,4-dichloro-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

EXAMPLE 185

30 5-Chloro-1-(1-{3-[3-(3,4-dichloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one

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EXAMPLE 186

1-{3-[4-(5-Methyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

5

EXAMPLE 187

3-(4-Bromo-phenyl)-1-{3-[4-(5-methyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

10

EXAMPLE 188

3-(4-Bromo-phenyl)-1-{3-[4-(6-ethanesulfonyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

15

EXAMPLE 187

1-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-3-[4-(5-trifluoromethyl-benzothiazol-2-yl)-piperidin-1-yl]-propan-2-ol

20

EXAMPLE 190

5-Methyl-4-(1-{3-[3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-benzo[1,4]oxazin-3-one

25 EXAMPLE 191

4-(1-{3-[3-(4-Bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-methyl-4H-benzo[1,4]oxazin-3-one

EXAMPLE 192

30 4-(1-{3-[3-(4-Bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-6-ethanesulfonyl-4H-benzo[1,4]oxazin-3-one

EXAMPLE 193

1-{3-[4-(6-Chloro-indol-1-yl)-piperidin-1-yl]-propyl}-5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine

5 EXAMPLE 194

3-(4-Bromo-phenyl)-1-{3-[4-(2-oxo-3,4-dihydro-2H-quinolin-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

10 EXAMPLE 195

3-(4-Bromo-phenyl)-1-{2-hydroxy-3-[4-(2-oxo-3,4-dihydro-2H-quinolin-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

15 EXAMPLE 196

3-(4-Bromo-phenyl)-1-{2-hydroxy-3-[4-(3-oxo-2,3-dihydro-1,4-benzoxazin-4-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

20 EXAMPLE 197

1-(1-{3-[3-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one

EXAMPLE 198

25 3-(4-Bromo-phenyl)-1-{3-[4-(3-oxo-2,3-dihydro-1,4-benzoxazin-4-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

EXAMPLE 199

30 1-(1-{2-Hydroxy-3-[3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one

EXAMPLE 200

4-(1-{3-[3-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-1,4-benzoxazin-3-one

5 EXAMPLE 201

1-(1-{3-[3-(4-Bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one

EXAMPLE 202

10 4-(1-{3-[3-(4-Bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-1,4-benzoxazin-3-one

EXAMPLE 203

15 1-(1-{3-[3-(4-Bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinolin-2-one

EXAMPLE 204

20 4-(1-{3-[3-(4-Bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-4H-1,4-benzoxazin-3-one

EXAMPLE 205

4-(1-{2-Hydroxy-3-[3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-4H-1,4-benzoxazin-3-one

25 EXAMPLE 206

1-(3-(3,4-Difluoro-phenyl)-1-{3-[4-(2,3-dihydro-indol-1-yl)-piperidin-1-yl]-2-hydroxy-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

EXAMPLE 207

30 1-[1-{3-[4-(5-Bromo-2,3-dihydro-indol-1-yl)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-chloro-3-methyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 208

1-(1-{3-[5-Acetyl-3-(3,4-difluoro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one

5 EXAMPLE 209

1-[1-{3-[4-(5-Bromo-2,3-dihydro-indol-1-yl)-piperidin-1-yl]-2-hydroxy-propyl}-3-(3,4-difluoro-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 210

10 1-(1-{3-[3-(4-Bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinazolin-2-one

EXAMPLE 211

15 1-(1-{3-[3-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinazolin-2-one

EXAMPLE 212

20 1-(1-{3-[3-(4-Bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3,4-dihydro-1H-quinazolin-2-one

EXAMPLE 213

1-(3-(4-Chloro-phenyl)-1-{3-[4-(3-chloro-phenylamino)-piperidin-1-yl]-2-hydroxy-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

25 EXAMPLE 214

N-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-N-(3-chloro-phenyl)-acetamide

EXAMPLE 215

30 1-(4-Benzoimidazol-1-yl-piperidin-1-yl)-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propan-2-ol

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EXAMPLE 216

1-(3-(4-Chloro-phenyl)-1-[2-hydroxy-3-[4-(2-methoxy-phenylamino)-piperidin-1-yl]-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

5 EXAMPLE 217

1-(3-(4-Chloro-phenyl)-1-[3-[4-(2-fluoro-phenylamino)-piperidin-1-yl]-2-hydroxy-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

EXAMPLE 218

10 1-[3-(4-Chloro-phenyl)-1-[2-hydroxy-3-(4-phenylamino-piperidin-1-yl)-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 219

15 1-(3-(4-Chloro-phenyl)-1-[3-[4-(4-chloro-phenylamino)-piperidin-1-yl]-2-hydroxy-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

EXAMPLE 220

20 1-[1-[3-[4-(4-Bromo-phenylamino)-piperidin-1-yl]-2-hydroxy-propyl]-3-(4-chloro-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 221

4-(1-[3-[5-Acetyl-3-(4-chloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl]-piperidin-4-ylamino)-benzonitrile

25 EXAMPLE 222

1-[3-(4-Chloro-phenyl)-1-[2-hydroxy-3-(4-p-tolylamino-piperidin-1-yl)-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 223

30 1-(3-(4-Chloro-phenyl)-1-[2-hydroxy-3-[4-(4-methoxy-phenylamino)-piperidin-1-yl]-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

EXAMPLE 224

1-(3-(4-Chloro-phenyl)-1-{2-hydroxy-3-[4-(3-methoxy-phenylamino)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

5 EXAMPLE 225

1-(3-(4-Chloro-phenyl)-1-{3-[4-(3,5-dimethoxy-phenylamino)-piperidin-1-yl]-2-hydroxy-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

EXAMPLE 226

10 1-[1-{3-[4-(5-Chloro-2-methyl-phenylamino)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-chloro-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 227

15 1-(3-(4-Chloro-phenyl)-1-{3-[4-(3-chloro-phenylamino)-piperidin-1-yl]-2-hydroxy-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

EXAMPLE 228

[2-(1-{3-[3-(4-Bromo-phenyl)-5-carbamoyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-ylamino)-4-ethanesulfonyl-phenoxy]-acetic
20 acid methyl ester

EXAMPLE 229

[2-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-ylamino)-4-ethanesulfonyl-phenoxy]-acetic acid methyl
25 ester

EXAMPLE 230

[2-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-ylamino)-4-ethanesulfonyl-phenoxy]-acetic acid methyl ester
30

EXAMPLE 231

3-(4-Bromo-phenyl)-1-{3-[4-(5-ethanesulfonyl-2-methoxycarbonylmethoxy-phenylamino)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

5

EXAMPLE 232

[2-(1-{3-[3-(4-Bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-ylamino)-4-ethanesulfonyl-phenoxy]-acetic acid methyl ester

10 EXAMPLE 233

1-{3-(4-Bromo-phenyl)-1-[2-hydroxy-3-(4-o-tolyloxy-piperidin-1-yl)-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl}-ethanone

EXAMPLE 234

15 1-{3-(4-Bromo-phenyl)-1-[2-hydroxy-3-(4-phenoxy-piperidin-1-yl)-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl}-ethanone

EXAMPLE 235

20 1-{3-(4-Bromo-phenyl)-1-[2-hydroxy-3-(4-p-tolyloxy-piperidin-1-yl)-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl}-ethanone

EXAMPLE 236

25 1-(3-(4-Bromo-phenyl)-1-{2-hydroxy-3-[4-(4-methoxy-phenoxy)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

EXAMPLE 237

1-(3-(4-Bromo-phenyl)-1-{3-[4-(4-chloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

30 EXAMPLE 238

1-(3-(4-Bromo-phenyl)-1-{3-[4-(3-chloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

EXAMPLE 239

1-(3-(4-Bromo-phenyl)-1-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

5 EXAMPLE 240

1-{3-(4-Chloro-3-methyl-phenyl)-1-[2-hydroxy-3-(4-phenoxy-piperidin-1-yl)-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl}-ethanone

EXAMPLE 241

10 1-{3-(4-Chloro-3-methyl-phenyl)-1-[2-hydroxy-3-(4-p-tolyloxy-piperidin-1-yl)-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl}-ethanone

EXAMPLE 242

15 1-(3-(4-Chloro-3-methyl-phenyl)-1-{2-hydroxy-3-[4-(4-methoxy-phenoxy)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

EXAMPLE 243

20 1-(3-(4-Chloro-3-methyl-phenyl)-1-{3-[4-(4-chloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

EXAMPLE 244

1-(3-(4-Chloro-3-methyl-phenyl)-1-{3-[4-(3-chloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

25 EXAMPLE 245

1-{3-(4-Chloro-3-methyl-phenyl)-1-[2-hydroxy-3-(4-o-tolyloxy-piperidin-1-yl)-propyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl}-ethanone

EXAMPLE 245

30 1-(3-(4-Chloro-3-methyl-phenyl)-1-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

EXAMPLE 246

2-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yloxy)-benzonitrile

5 EXAMPLE 247

2-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yloxy)-benzonitrile

EXAMPLE 248

10 1-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-3-[4-(4-chloro-phenoxy)-piperidin-1-yl]-propan-2-ol

EXAMPLE 249

15 1-[1-{3-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 250

20 1-(1-{3-[5-Acetyl-3-(4-chloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 251

1-(1-[3-(5-Acetyl-3-phenyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl)-2-hydroxy-propyl]-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

25 EXAMPLE 252

1-(1-{3-[5-Acetyl-3-(4-trifluoromethoxy-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

30 EXAMPLE 253

1-(1-{3-[5-Acetyl-3-(4-iodo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 254

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

5

EXAMPLE 255

1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

10 EXAMPLE 256

1-(1-{3-[5-Acetyl-3-(4-chloro-3-nitro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

15 EXAMPLE 257

1-(1-{3-[5-Acetyl-3-(4-trifluoromethylsulfanyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

20 EXAMPLE 258

1-(1-{3-[5-Acetyl-3-(4-methanesulfonyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

25 EXAMPLE 259

1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-1,3-dihydro-benzoimidazol-2-one

30 EXAMPLE 260

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 261

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-ethyl-1,3-dihydro-
5 benzoimidazol-2-one

EXAMPLE 262

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-isopropyl-1,3-dihydro-
10 benzoimidazol-2-one

EXAMPLE 263

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-butyl-1,3-dihydro-
15 benzoimidazol-2-one

EXAMPLE 264

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-benzyl-1,3-dihydro-
20 benzoimidazol-2-one

EXAMPLE 265

1-(1-{3-[5-Acetyl-3-(4-iodo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-fluoro-1,3-dihydro-benzoimidazol-2-one
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EXAMPLE 266

3-(1-{3-[5-Acetyl-3-(4-iodo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-7-fluoro-2-oxo-2,3-dihydro-1H-benzoimidazole-4-carbonitrile
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EXAMPLE 267

1-(1-{3-[5-Acetyl-3-(4-iodo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-fluoro-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 268

3-(1-{3-[5-Acetyl-3-(4-iodo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-1H-benzoimidazole-5-carbonitrile

EXAMPLE 269

1-{2-Hydroxy-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide

EXAMPLE 270

1-(1-{3-[3-(4-Chloro-3-methyl-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 271

3-(4-Chloro-3-methyl-phenyl)-1-{2-hydroxy-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid methylamide

EXAMPLE 272

3-(4-Chloro-3-methyl-phenyl)-1-{2-hydroxy-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid ethylamide

EXAMPLE 273

1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-methyl-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 274

1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-methyl-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 275

1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5,6-dichloro-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 276

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-methyl-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 277

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-methyl-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 278

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5,6-dichloro-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 279

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 280

1-(1-{3-[5-Acetyl-3-(4-chloro-3-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 281

1-(1-{3-[3-(4-Chloro-3-methyl-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-(2-morpholin-4-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one

10

EXAMPLE 282

1-(1-{3-[5-Acetyl-3-(3-fluoro-4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 283

1-(1-{3-[5-Acetyl-3-(4-bromo-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 284

(*R*)-1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 285

1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-methoxy-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 286

1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-7-chloro-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 287

3-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

10 EXAMPLE 288

1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-7-methyl-1,3-dihydro-benzoimidazol-2-one

15 EXAMPLE 289

(*R*)-1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-1,3-dihydro-benzoimidazol-2-one

20 EXAMPLE 290

1-(1-{3-[5-Acetyl-3-(3,4-dichloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

25 EXAMPLE 291

1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 292

30 1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 293

(S)-1-(1-(3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl)-piperidin-4-yl)-6-chloro-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 294

(R)-1-(1-(3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl)-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

10

EXAMPLE 295

(R)-1-(1-(3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl)-piperidin-4-yl)-6-chloro-1,3-dihydro-benzoimidazol-2-one

15

EXAMPLE 296

2-{2-[3-(1-(3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl)-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-ethyl}-isoindole-1,3-dione

20

EXAMPLE 297

1-(1-(3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl)-piperidin-4-yl)-3-(2-amino-ethyl)-1,3-dihydro-benzoimidazol-2-one

25

EXAMPLE 298

1-(1-(3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl)-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

30

EXAMPLE 299

1-(1-(3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl)-piperidin-4-yl)-3-ethyl-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 300

1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-
c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-
5 benzoimidazol-2-one

EXAMPLE 301

1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-
c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-ethyl-1,3-dihydro-
10 benzoimidazol-2-one

EXAMPLE 302

6-Chloro-1-(1-{3-[3-(4-chloro-3-methyl-phenyl)-5-methanesulfonyl-4,5,6,7-
tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-
15 dihydro-benzoimidazol-2-one

EXAMPLE 303

1-(1-{3-[5-Acetyl-3-(3-chloro-4-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-
c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-
20 one

EXAMPLE 304

3-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-
c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-chloro-1-(2-morpholin-4-yl-
25 ethyl)-1,3-dihydrobenzoimidazol-2-one

EXAMPLE 305

[3-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-
c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-
30 benzoimidazol-1-yl]-aceticacid ethyl ester

EXAMPLE 306

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-(2,2,2-trifluoro-ethyl)-1,3-dihydrobenzoimidazol-2-one

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EXAMPLE 307

[3-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]acetonitrile

10

EXAMPLE 308

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-(2-hydroxy-ethyl)-1,3-dihydro-benzoimidazol-2-one

15

EXAMPLE 309

1-(1-{3-[5-Acetyl-3-(3-chloro-4-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-chloro-1,3-dihydro-benzoimidazol-2-one

20

EXAMPLE 310

1-(1-{3-[5-Acetyl-3-(3-chloro-4-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

25

EXAMPLE 311

1-Ethyl-3-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 312

1-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

5

EXAMPLE 313

1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-(2-hydroxy-ethyl)-1,3-dihydro-benzoimidazol-2-one

10

EXAMPLE 314

3-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

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EXAMPLE 315

[3-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-acetonitrile

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EXAMPLE 316

2-[3-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-acetamide

25

EXAMPLE 317

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-(2-oxo-tetrahydro-furan-3-yl)-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 318

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-(2-methoxy-ethyl)-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 319

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-(2-oxo-butyl)-1,3-dihydro-benzoimidazol-2-one

10

EXAMPLE 320

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-(2-diethylamino-ethyl)-1,3-dihydro-benzoimidazol-2-one

15

EXAMPLE 321

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-cyclopropylmethyl-1,3-dihydro-benzoimidazol-2-one

20

EXAMPLE 322

1-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-(2-methyl-allyl)-1,3-dihydro-benzoimidazol-2-one

25

EXAMPLE 323

1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-methyl-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 324

5-Chloro-3-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-benzoimidazol-2-one

5

EXAMPLE 325

6-Chloro-1-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 326

N-[4-(5-Acetyl-1-{2-hydroxy-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-3-yl)-phenyl]-acetamide

15

EXAMPLE 327

[3-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-acetic acid

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EXAMPLE 328

1-(1-{3-[5-Acetyl-3-(3-bromo-4-chloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

25

EXAMPLE 329

3-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

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EXAMPLE 330

3-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

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EXAMPLE 331

1-(1-{3-[5-(1H-Imidazole-4-carbonyl)-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

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EXAMPLE 332

1-{3-[4-(3-Methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide

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EXAMPLE 333

1-{3-[4-(3-Methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid ethylamide

20

EXAMPLE 334

1-(1-{3-[5-(Isoxazole-5-carbonyl)-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

25

EXAMPLE 335

1-{3-[4-(3-Methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-sulfonic acid (N-t-butoxycarbonyl)amide

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EXAMPLE 336

1-Methyl-3-(1-{3-[5-(5-methyl-isoxazole-3-carbonyl)-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

5

EXAMPLE 337

3-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-methoxy-1-methyl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

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EXAMPLE 338

3-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-methoxy-1-methyl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

15

EXAMPLE 339

5-Dimethylamino-3-(1-{3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

20

EXAMPLE 340

3-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-ethyl-5-methoxy-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

25

EXAMPLE 341

1-(1-{3-[5-Acetyl-3-(4-nitro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

30

EXAMPLE 342

1-(1-{3-[5-Acetyl-3-(4-nitro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 343

3-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-ethyl-5-methoxy-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

5

EXAMPLE 344

3-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-methoxy-1-methyl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

10

EXAMPLE 345

1-{3-[4-(3-Methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid benzyl ester

15

EXAMPLE 346

5-Dimethylamino-3-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

20

EXAMPLE 347

1-{3-[4-(3-Methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carbothioic acid methylamide

25

EXAMPLE 348

3-(4-Bromo-phenyl)-1-{3-[4-(3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid phenylamide

30

EXAMPLE 349

1-(1-{3-[5-Benzoyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 350

1-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

5

EXAMPLE 351

1-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

10

EXAMPLE 352

3-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-chloro-1-methyl-1,3-dihydro-benzoimidazol-2-one

15

EXAMPLE 353

1-{3-[4-(6-Chloro-3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide

20

EXAMPLE 354

1-(1-{3-[3-(4-Bromo-phenyl)-5-phenylmethanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

25

EXAMPLE 355

1-(1-{3-[5-Acetyl-3-(3,4-dichloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

30

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EXAMPLE 356

3-(4-Bromo-phenyl)-1-{3-[4-(3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide

5

EXAMPLE 357

3-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-chloro-1-methyl-1,3-dihydro-benzoimidazol-2-one

10 EXAMPLE 358

3-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-chloro-1-methyl-1,3-dihydro-benzoimidazol-2-one

15 EXAMPLE 359

3-(4-Bromo-phenyl)-1-{3-[4-(6-chloro-3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide

20 EXAMPLE 360

3-(1-{3-[5-Methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,5-dimethyl-1,3-dihydro-benzoimidazol-2-one

25 EXAMPLE 361

1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 362

30 3-(4-Bromo-phenyl)-1-{3-[4-(3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-sulfonic acid t-butoxycarbonyl-amide

EXAMPLE 363

1-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

5 EXAMPLE 364

1-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 365

10 3-(4-Bromo-phenyl)-1-{3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-sulfonic acid t-butoxycarbonyl-amide

EXAMPLE 366

15 3-(4-Bromo-phenyl)-1-{3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide

EXAMPLE 367

20 (R)-5-Chloro-3-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 368

25 1-(1-{3-[5-Acetyl-3-(3,4-dichloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 369

30 1-(1-{3-[3-(3,4-Dichloro-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 370

1-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-methoxy-1,3-dihydro-benzoimidazol-2-one

5

EXAMPLE 371

3-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

10

EXAMPLE 372

3-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-methoxy-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

15

EXAMPLE 373

1-{2-Hydroxy-3-[4-(2-oxo-1,2-dihydro-imidazo[4,5-b]pyridin-3-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide

20

EXAMPLE 374

3-(4-Bromo-phenyl)-1-{2-hydroxy-3-[4-(2-oxo-1,2-dihydro-imidazo[4,5-b]pyridin-3-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid amide

25

EXAMPLE 375

[3-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-imidazo[4,5-b]pyridin-1-yl]-acetonitrile

30

EXAMPLE 376

3-(3,4-Dichloro-phenyl)-1-{3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid methylamide

5

EXAMPLE 377

3-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

10 EXAMPLE 378

3-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-5-methoxy-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

15 EXAMPLE 379

[3-(1-{3-[3-(4-Bromo-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-acetic acid ethyl ester

20 EXAMPLE 380

[3-(1-{3-[5-Acetyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-acetic acid ethyl ester

25 EXAMPLE 381

[3-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-acetic acid ethyl ester

30 EXAMPLE 382

5-Chloro-3-(1-{3-[3-(3,4-dichloro-phenyl)-5-methanesulfonyl-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 383

(R)-1-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 384

1-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3-pyridin-4-ylmethyl-1,3-dihydro-benzoimidazol-2-one

EXAMPLE 385

(R)-5-Dimethylamino-3-(1-{2-hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-1-methyl-1,3-dihydro-imidazo[4,5-b]pyridin-2-one

EXAMPLE 386

3-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-chloro-3H-benzooxazol-2-one

EXAMPLE 387

3-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-4-methyl-3H-benzooxazol-2-one

EXAMPLE 388

3-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzooxazole-6-carboxylic acid ethyl ester

EXAMPLE 389

3-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-ethanesulfonyl-3H-benzooxazol-2-one

EXAMPLE 390

3-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-4-methyl-3H-benzooxazol-2-one

5 EXAMPLE 391

3-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-2-oxo-2,3-dihydro-benzooxazole-6-carboxylic acid ethyl ester

10 EXAMPLE 392

3-(1-{3-[5-Acetyl-3-(4-bromo-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-methoxy-3H-benzooxazol-2-one

EXAMPLE 393

15 3-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-ethanesulfonyl-3H-benzooxazol-2-one

EXAMPLE 394

20 3-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-6-methoxy-3H-benzooxazol-2-one

EXAMPLE 395

25 3-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-3H-benzooxazol-2-one

EXAMPLE 396

30 3-(1-{3-[5-Acetyl-3-(4-chloro-3-methyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-2-hydroxy-propyl}-piperidin-4-yl)-5-chloro-3H-benzooxazol-2-one

EXAMPLE 397

3-(1-{2-Hydroxy-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propyl}-piperidin-4-yl)-3H-oxazolo[4,5-b]pyridin-2-one

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EXAMPLE 398

1-[1-[3-(4-Benzooxazol-2-yl-piperidin-1-yl)-2-hydroxy-propyl]-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

10 EXAMPLE 399

1-[1-{2-Hydroxy-3-[4-(6-methyl-benzooxazol-2-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 400

15 1-[1-{3-[4-(Benzothiazol-2-yloxy)-piperidin-1-yl]-2-hydroxy-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 401

20 1-[1-{2-Hydroxy-3-[4-(5-methyl-benzooxazol-2-yl)-piperidin-1-yl]-propyl}-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 402

1-(3-(4-Chloro-phenyl)-1-{2-hydroxy-3-[4-(2-methoxy-phenyl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-ethanone

25

EXAMPLE 403

3-(4-Chloro-phenyl)-1-{2-hydroxy-3-[4-(2-methoxy-phenyl)-piperidin-1-yl]-propyl}-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carbaldehyde

30 EXAMPLE 404

1-[1-[3-(4-Benzo[b]thiophen-2-yl-piperidin-1-yl)-2-hydroxy-propyl]-3-(4-trifluoromethyl-phenyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone

EXAMPLE 405

1-[4-(6-Chloro-indol-1-yl)-piperidin-1-yl]-3-[5-methanesulfonyl-3-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-1-yl]-propan-2-ol

5

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Table 3

EXAMPLE	IC ₅₀ (μM)
101	0.51
104	0.12
106	0.06
110	0.33
111	1.2
113	0.11
114	0.10
117	0.28
116	0.64
119	0.09
122	0.06
125	0.25
126	0.08
127	0.02
130	0.03
132	0.11
133	0.15
137	0.03
139	0.13
141	0.84
143	0.05
145	0.07
148	0.13
149	0.13
154	0.09
155	0.04
157	0.04
159	0.15

EXAMPLE (Table 3, cont'd)	IC ₅₀ (μM) (Table 3, cont'd)
160	0.15
163	0.14
167	0.13
168	0.16
169	0.09
171	0.16
174	0.85
176	0.83
177	0.05
180	0.09
182	0.87
183	2.3
188	1.1
187	0.36
193	0.44
195	1.1
197	1.4
207	1.3
211	1.8
213	1.1
215	0.14
217	0.83
221	1.4
226	0.75
228	0.17
233	0.34
236	0.71
239	0.34
244	0.65

EXAMPLE (Table 3, cont'd)	IC ₅₀ (μM) (Table 3, cont'd)
246	0.30
249	0.69
252	0.13
253	0.14
256	0.64
257	0.26
258	0.23
259	0.12
260	0.48
261	0.35
264	0.34
266	0.66
267	0.28
268	0.30
269	0.12
270	0.04
272	0.33
273	0.09
275	0.12
277	0.06
280	0.23
281	0.33
284	0.26
285	0.13
286	0.21
289	0.20
290	0.15
293	0.16
294	0.28

EXAMPLE (Table 3, cont'd)	IC ₅₀ (μM) (Table 3, cont'd)
296	0.34
300	0.14
301	0.18
304	0.14
305	0.11
306	0.09
307	0.09
308	0.13
313	0.23
314	0.14
315	0.08
316	0.28
320	0.39
321	0.08
325	0.09
327	0.52
329	0.08
330	0.06
331	0.06
333	0.24
334	0.08
335	0.39
336	0.16
337	0.10
339	0.20
340	0.09
342	0.38
345	0.55
346	0.07

EXAMPLE (Table 3, cont'd)	IC ₅₀ (μM) (Table 3, cont'd)
347	0.48
348	0.19
354	0.93
359	0.04
365	0.11
366	0.05
367	0.03
371	0.08
374	0.08
375	0.05
379	0.07
383	0.18
384	0.17
385	0.04
386	0.37
387	0.34
388	0.32
392	0.27
395	0.39
396	0.31
397	0.12
398	0.19
399	0.51
400	0.55
401	0.32

5

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What is claimed is:

Variable	Mean		SD		t		p	
	Control	Case	Control	Case	Control	Case	Control	Case
Age	21.5	21.5	1.5	1.5	0.0	0.0	0.999	0.999
Gender	10	10	0	0	0.0	0.0	0.999	0.999
Height	170.0	170.0	5.0	5.0	0.0	0.0	0.999	0.999
Weight	60.0	60.0	10.0	10.0	0.0	0.0	0.999	0.999
Education	12.0	12.0	0.0	0.0	0.0	0.0	0.999	0.999
Occupation	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Marital status	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Religion	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Income	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Health status	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Family size	3.0	3.0	1.0	1.0	0.0	0.0	0.999	0.999
Parental education	12.0	12.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental occupation	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental marital status	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental religion	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental income	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental health status	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental family size	3.0	3.0	1.0	1.0	0.0	0.0	0.999	0.999
Parental parental education	12.0	12.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental occupation	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental marital status	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental religion	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental income	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental health status	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental family size	3.0	3.0	1.0	1.0	0.0	0.0	0.999	0.999
Parental parental parental education	12.0	12.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental occupation	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental marital status	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental religion	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental income	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental health status	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental family size	3.0	3.0	1.0	1.0	0.0	0.0	0.999	0.999
Parental parental parental parental education	12.0	12.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental parental occupation	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental parental marital status	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental parental religion	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental parental income	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental parental health status	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental parental family size	3.0	3.0	1.0	1.0	0.0	0.0	0.999	0.999
Parental parental parental parental parental education	12.0	12.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental parental parental occupation	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental parental parental marital status	1.0	1.0	0.0	0.0	0.0	0.0	0.999	0.999
Parental parental parental parental parental religion	1.0	1.						